Around isocyanide reactivity: Development of enantioselective transformations and syntheses of heterocycles and natural products

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“Those who do not want to imitate anything, produce nothing”

- Salvador Dalí

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Résumé

Deux principaux sujets ont été décrits dans ce manuscrit. La première partie traite de la réaction de Michael organocatalique et énantiosélective de différents donneurs de Michael avec la phenyl vinyl selenone. D'un côté les nitroacetates α-substitués ont été utilisés comme donneurs de Michael. En présence de dérivés d'alkaloides du *quinquina* comme organocatalyseur, la synthèse de dérivés d'amino-acides quaternaires enantioenrichis a été possible. D'un autre côté, les nitroamides α-substitué ont aussi été utilisés comme partenaires dans cette réaction. Avec eux, une séquence d'addition de Michael organocatalytique suivie d'une S_N2 intramoléculaire et d'une hydrolyse a été développée pour la synthèse de γ-lactone avec une enantiosélectivité modérée. La deuxième partie est focalisée sur l'insertion de différent isocyanures catalysés par des métaux de transition pour la synthèse de produits naturels et d'heterocycles variés. Dans un premier temps nous avons développé la synthèse de imidazolones-3,5,5-trisubstitués en utilisant l'insertion de α,α-dibenzyl α-isocyanoacetate avec une amine primaire catalysée par du nitrate d'argent. Avec cette même méthodologie, evodiamine et rutaecarpine, deux produits naturels, ont été synthétisés à partir de l'*o*-isocyanobenzoate de méthyle. La synthèse de imidazolones-2,3,5,5-tetrasubstitués a aussi été reportée par l'utilisation de la réaction trois-composantes de α,α-dibenzyl α-isocyanoacetate, d'une amine primaire et d'iodure d'aryle en présence d'un système bimetallique palladium/cuivre. Dans un second temps, l'insertion d'isocyanure catalysé par du palladium a été étudiée. La réaction multicomposante d'une amine primaire, d'un iodure d'aryle et de l'*o*-cyanobenzonitrile catalysée par du palladium a permis l'élaboration de quinazolin-4-one 2-substitué. Finalement, le procédé domino catalysé par du palladium entraine l'insertion d'isocyanure et l'activation $C(sp)^3$-H du 3-cyclopropyl-2-isocyanopropanoate pour fournir un azaspiro[2.4]hept-4-ene C-2 arylé.

Mots clés: *organocatalyse, phenyl vinyl selenone, amino acide quaternaire, nitroacetate, nitroamide, alkaloide du quinquina, insertion d'isonitrile, , α,α-disbustittued isocyanoacetate, imidazolone, quinazolin-4-one, reaction multicomposantes, procédé domino.*

Abstract

This manuscript covers two main topics. The first part dealt with the organocatalytic conjugate addition of Michael donors to phenyl vinyl selenone. The enantioselective *Cinchona* alkaloid-catalyzed Michael addition using α-substituted α-nitroacetates has been developed. The synthesis of various α,α-dialkyl α-nitroacetates has been accomplished in excellent yield and good enantioselectivity which were subsequently converted to cyclic and acyclic quaternary α–amino acids, taking advantage of the rich functionalities of the adducts. α-Substituted α-nitroamides have also been utilized as nucleophile. With them, an organocatalytic Michael addition/intermolecular S_N2/hydrolysis sequence have been developed for the synthesis of γ-lactones in moderate enantioselectivity. The second part of the manuscript focused on the transition-metal-catalysed insertion of isocyanides bearing participating functional group for the synthesis of heterocycles and natural product. On the one hand, the synthesis of 3,5,5-trisubstituted imidazolones using silver-catalyzed reaction of α,α-disubstituted α-isocyanoacetate with primary amine have been developed. To illustrate this methodology, evodiamine and rutaecarpine, two natural products, have been synthesized using methyl *o*-isocyanobenzoate. The synthesis of 2,3,5,5-tetrasubstituted imidazolones have been also reported using the 3-CR reaction of α,α-dibenzyl α-isocyanoacetate, primary amine and aryl iodide in the presence of a palladium/copper bimetallic system. On the other hand, palladium catalysed isocyanide insertion have been explored. The Pd-catalyzed multicomponent reaction of primary amine, aryl halide and *o*-cyanobenzonitrile has permitted the construction of 2-substituted quinazolin-4-one. Finally, the Pd-catalyzed domino process isocyanide insertion/$C(sp)^3$-H activation of 3-cyclopropyl-2-isocyanopropanoate furnished C-2 arylated azaspiro[2.4]hept-4-ene.

Key words: *Organocatalysis, phenyl vinyl selenone, quaternary amino acids, nitroacetate, nitroamide, cinchona, isocyanide insertion, α,α-disbustittued isocyanoacetate, imidazolone, quinazolin-4-one, multicomponent reaction, domino process.*

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Abbreviations list

°C	degree Celsius
α_D	Specific rotation
Ac	Acetyl
AcOEt	Ethyl acetate
aq	Aqueous
Ar	Aromatic
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	tert-butyloxycarbonyl
box	bis-oxozolidine
BQ	Benzoquinone
brsm	Based on recovered starting material
BSA	Benzene seleninic anhydride
Bu	Butyl
Bz	Benzoyl
Cat*	Chiral catalyst
Cbz	Carboxybenzyl
Cf.	Confer
cod	Cyclooctadiene
conc	Concentration
conv	Conversion
CR	(3-CR) Component reaction
CSA	Camphorsulfonic acid
d	Day
D or (+)	Dextrorotary
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DFT	Density Functional Theory
DIBAL-H	Diisobutylaluminium hydride
DIAD	Diisopropyl azadicarboxylate
DIEA	Diisopropylethylamine
dig	Digonal
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMB	Dimethoxybenzyl
DME	Dimethoxyethane
DMF	Demthylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethylsulfoxide

DPP	N-diphenylphosphinoyl
DPPA	Diphenylphosphoryl azide
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
E or E^+	Electrophile
E	Entgegen
ee	Enantiomeric excess
eq.	Equation
equiv.	Equivalent
er	enantiomeric ratio
Et	Ethyl
EWG	Electron withdrawing group
FCC	Flash Column Chromatography
FG	Functional group
FGI	Functional group interconversion
g	Gram
GFP	Green fluorescent probe
h	Hour
hex	Hexyl
HIV	Human immunodeficiency virus
HMDS	Bis(trimethylsilyl)amine
HMPA	Hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
hν	Light
Hz	Hertz
IBX	2-iodoxybenzoic acid
ICD	Isocupreidine
i-Pr	Isopropyl
L or (-)	Levorotary
L*	Chiral ligand
LA	Lewis Acid
LDA	Lithium diisopropylamide
LTMP	Lithium tetramethylpiperidide
m	*meta*
M	Molar
m-CPBA	meta-Chloroperoxybenzoic acid
MCR	Multi-component reaction
Me	Methyl
min	Minutes
mmol	milimole
MMTr	Monomethoxy trityl
mol	Mole
MOM	methoxymethyl ether
Ms	Mesyl
MS	Molecular sieves

μW	Microwave
N	Normal
NBS	N-Bromosuccinimide
n-Bu	normal-butyl
NHC	N-Heterocyclic carbene
NMO	N-Methylmorpholine N-oxide
NMR	Nuclear Magnetic resonance
nr	No reaction
Nu or Nu^-	Nucleophile
o	*ortho*
p	*para*
Pa	Pascal
PE	Petroleum ether
PFP	Pentafluorophenyl
PG	Protecting group
Ph	Phenyl
PhD	Doctor of philosophy
Phth	Phthalimide
Pin	Pinacol or 2,3-dimethyl-2,3-butanediol
PMB	para-Methoxybenzyl
PPA	Polyphosphoric acid
PPTS	Pyridinium para-toluenesulfonate
Pr	Propyl
Precat*	Chiral precatalyst
PTC	Phase transfer catalysis
PTSA	para-Toluenesulfonic acid
pyr.	Pyridine
quant.	Quantitatif
R	Rectus
Red. El.	Reductive elimination
resp.	Respectively
RT	Room temperature
S	Sinister
SFC	Supercritical Fluid Chromatography
S_N (1 or 2)	Nucleophilic substitution
S_NAr	nucleophilic aromatic substitution
t Am	2-Methylbutan-2-ol
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBAT	Tetrabutylammonium difluorotriphenylsilicate
TBS	tert-Butyldimethylsilyl
t-Bu	tert-Butyl
tet	Tetragonal
Tf	Triflate
TFAA	Trifluoroacetic anhydride
TFA	Trifluoroacetic acid

TFE	Trifluoroethanol
THF	Tetrahydrofuran
TI	Therapeutic index
TBDMS	*tert*-Butyldimethylsilyl ether
TBDPS	*tert*-Butyldiphenylsilyl ether
TMS	Trimethylsilyl
TNF	(TNFα) Tumor necrosis factors
trig	Trigonal
Ts	Tosyl
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Xphos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
Z	Zusammen

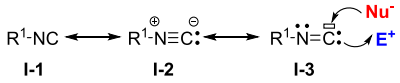
<u>Part I:</u> Development of Enantioselective Michael Additions Using Phenyl Vinyl Selenone

Chapter 1: α-Substituted α-Nitroacetate as Michael Donor

Coming through the project

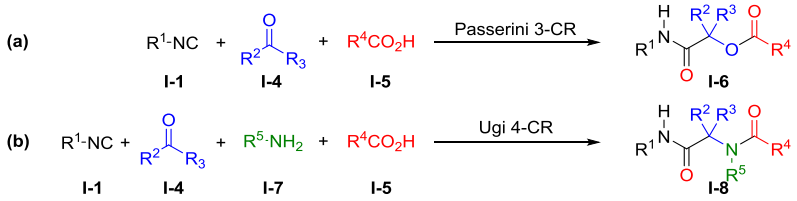
From isocyanide…

Isocyanide, named also as isonitrile, is an important reactive group in chemistry. With its resonance forms,[1] the isocyanide group has been generally represented as a polarized triple bond (Scheme 1, **I-2**) or as carbene-like molecule with a free lone pair on the carbon (Scheme 1, **I-3**). This particular hybridization has offered to this moiety the ability of reacting rapidly with an electrophile and a nucleophile almost simultaneously.



Scheme 1: isocyanide classical reactivity.

Firstly isolated by Lieke in 1859,[2] the isocyanide was popularized in the middle of the 20th century with the discovery of multicomponent reactions. In 1921, Passerini described the three component reaction (P-3CR, Scheme 2 **(a)**) [3] of carboxylic acid **I-5**, carbonyl **I-4** and isocyanide **I-1** whereas Ugi reported in 1961 the four component reaction (U-4CR, Scheme 2 **(b)**)[4] where an amine **I-7** reacted with the same adducts used in the P-3CR to give bis-amides **I-8**.[5] With the multiple possibilities of adducts association, various complex molecules could be constructed in one step from readily available starting material.[6]



Scheme 2: (a) Passerini three component reaction, (b) Ugi four component reaction.

Application of the isocyanide chemistry has been largely investigated. From hetereocycle synthesis to polymer construction, through to carbene-ligand design and natural product synthesis;[7] numerous fields have been impacted by this chemistry. In organic

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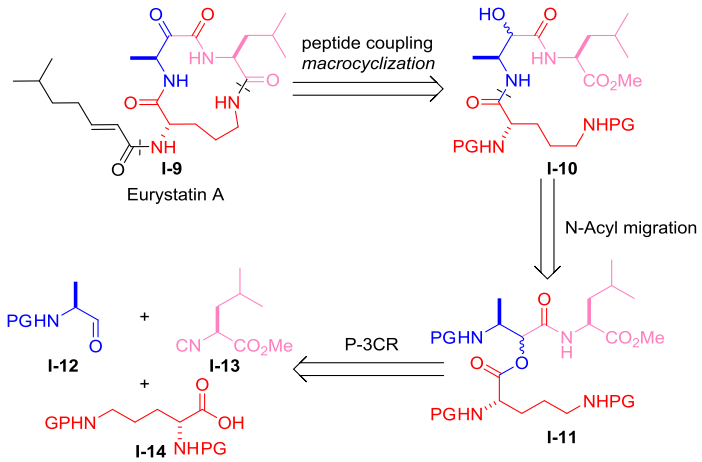
[1] R. Ramozzi, N. Chéron, B. Braida, P. C. Hiberty, P. Fleurat-Lessard, *New J. Chem.* **2012**, *36*, 1137.
[2] W. Lieke, *Justus Liebigs Ann. Chem.* **1859**, *112*, 316.
[3] (a) M. Passerini, *Gazz. Chim. Ital.* **1921**, *51*, 126; (b) M. Passerini, *Gazz. Chim. Ital.* **1921**, *51*, 181; (c) M. Passerini, G., Ragni, *ibid.* **1931**, *61*, 964.
[4] (a) I. Ugi, C. Steinbrückner, *Chem. Ber.* **1961**, *94*, 734-742; (b) I. Ugi, C. Steinbrückner, *Chem. Ber.* **1961**, *94*, 2802; (c) I. Ugi, *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 8.
[5] For more details on the history of isocyanide chemistry, see: I. Ugi, B. Werner, A Dömling, *Molecules* **2003**, *8*, 53.
[6] (a) A. Dömling, I. Ugi *Angew. Chem. Int. Ed.* **2000**, *39*, 3168; (b) J. Zhu, *Eur. J. Org. Chem.* **2003**, *2003*, 1133; (c) J. Zhu, H. Bienaymé, *Multicomponent Reactions, Wiley-VCH, Weinheim, Germany*, **2005**; J. Zhu, Q. Wang, M.X. Wang, *Multicomponent Reactions in Organic Synthesis, Wiley-VCH*, **2014**.
[7] V. G. Nenajdenko, *Isocyanide Chemistry: Application in Synthesis and Material Science, Wiley-VCH*, **2012.**

chemistry, the art of retrosynthesis using isocyanide-based MCR has been challenging but several research groups have developed impressive total synthesis with this isocyanide chemistry.

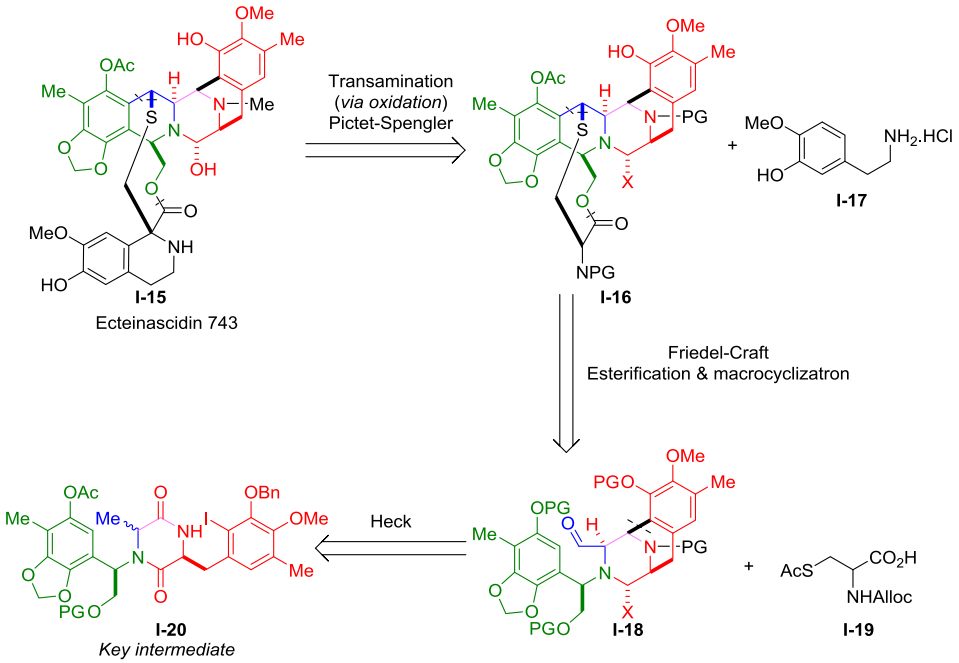
The total synthesis of Eurystatin A (**I-9**) by Semple and coworkers in 2001 is a good example of isocyanide-based MCR utilization.[8] This natural macrocycle was synthesized with a late peptide coupling of **I-10**. This linear peptide precursor **I-10** was formed via *N*-acyl migration of the ester intermediate **I-11**. **I-11**, was constructed concisely using the Passerini-3CR of alaninal **I-12**, leucine isonitrile **I-13**, and ornithine derivative **I-14 (**Scheme 3**)**.



Scheme 3: Semple's retrosynthesis for the total synthesis of Eurystatin A starting from P-3CR.

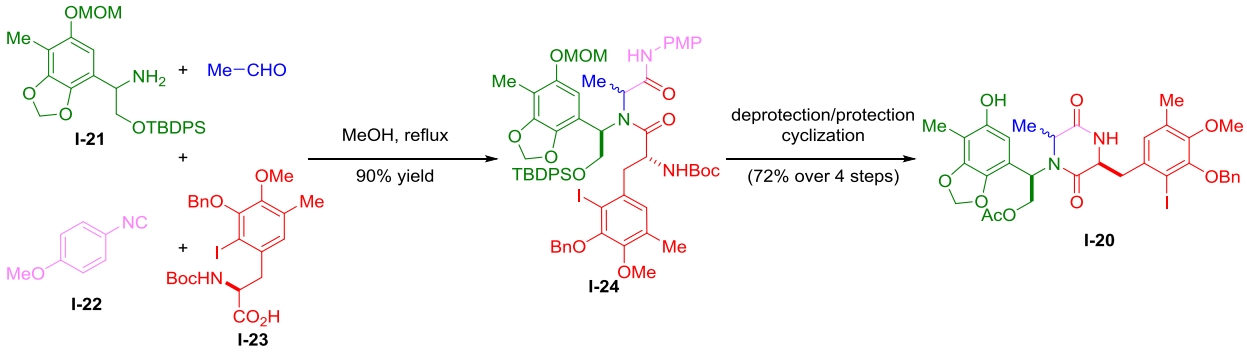
Ecteinascidin 743 (**I-15**), also known as Trabectedin, is an anti-tumor drug. Firstly synthesized by Corey,[9] Fukuyama has also highlighted the use of the isocyanide chemistry in the beautiful total synthesis of this natural product.[10] Ecteinascidin 743 was obtained using the same end-game strategy as Corey reported involving oxidation and Pictet Spengler reaction of **I-16**. The ten-membered sulfide was constructed by a sequential Friedel-Craft, esterification and macrocyclization of the intermediate **I-18** with the cysteine derivative **I-19**. The aldehyde **I-18** was isolated from the key intermediate **I-20** after an intramolecular Heck reaction and functional group modification (Scheme 4).

[8] T. D. Owens, G.-L. Araldi, R. F. Nutt, J. E. Semple, *Tetrahedron Lett.* **2001**, *42*, 6271.
[9] E. J. Corey, D. Y. Gin, R. S. Kania, *J. Am. Chem. Soc.* **1996**, *118*, 9202.
[10] A. Endo, A., Yanagisawa, M., Abe, S., Tohma, T., Kan, T. Fukuyama, *J. Am. Chem. Soc.* **2002**, *124*, 6552.



Scheme 4: Fukuyama's retrosynthesis approach for the Total Synthesis of Ecteinascidin 743.

The key framework **I-20** was synthesized in few steps *via* an Ugi 4 component reaction (Scheme 5). Ethanal, 1-isocyano-4-methoxybenzene **I-22**, amine **I-21** and amino acid **I-23** reacted in methanol under reflux to deliver **I-24** in 90% yield. After deprotection/protection/cyclization sequence, the key cyclic dipeptide **I-20** was isolated in 72% yield over 4 steps.

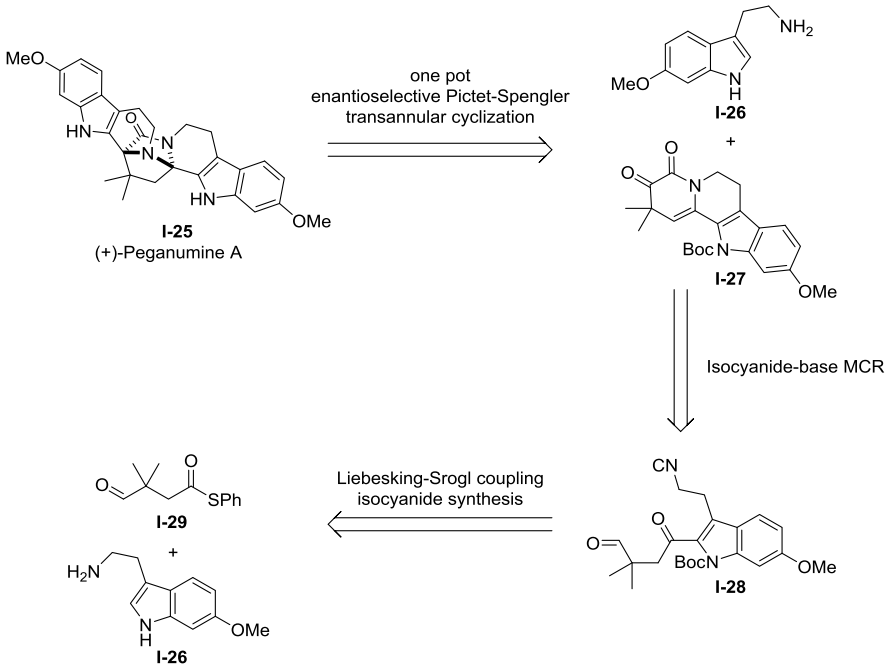


Scheme 5: Synthesis of the key intermediate via U-4CR.

Our group has been exploring the isocyanide reactivity for years and with a common affection for natural product total synthesis, some potent synthetic targets have been architected using isonitrile properties. The most recent example is the efficient 7 steps first total synthesis of (+)-Peganumine A (**I-25**) which was reported last year.[11] (+)-Peganumine A was accomplished *via* a one pot enantioselective Pictet-Spengler/Brønsted acid-catalyzed transannular cyclization of the commercially available 6-methoxytriptamine **I-26** and the

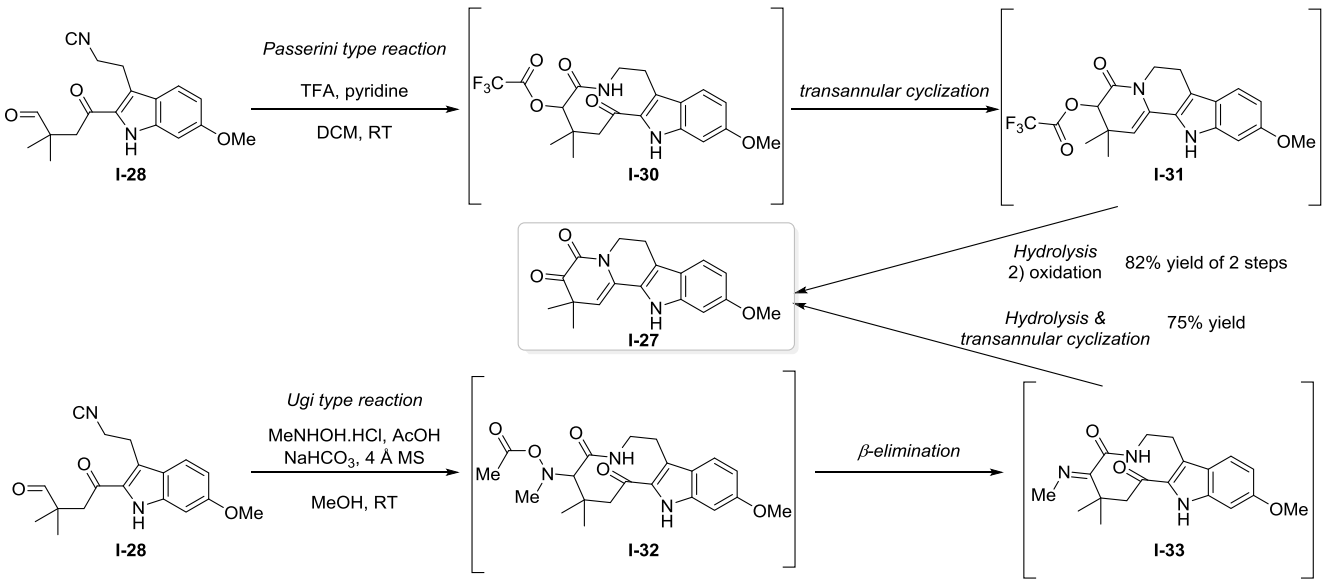
[11] C. Piemontesi, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2016**, *138*, 11148.

tetracyclic intermediate **I-27**. This tetracyclic core was synthesized by an isocyanide-base MCR of the isonitrile compound **I-28** which was obtained from the Liebesking-Srogl coupling of **I-29** and the isocyanide derivative of 6-methoxytriptamine **I-30** (Scheme 6).



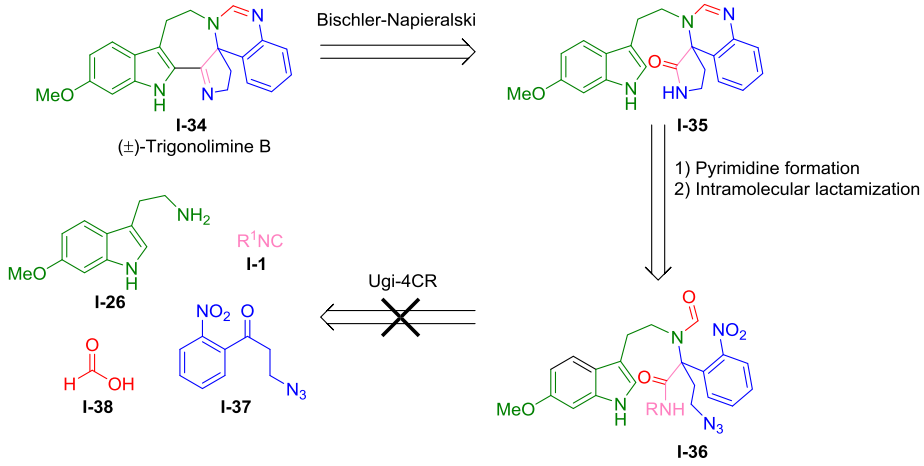
Scheme 6: (+)-Peganumine A: our retrosynthesis.

Two different multicomponent reactions to synthesize the key intermediate **I-27** have been developed. The Passerini reaction of **I-28**, TFA and pyridine in DCM at room temperature offered the ten-membered lactam **I-30**. After transannular cyclization of the amide group on the carbonyl, the tetracyclic structure was formed to give the molecule **I-31**. Deprotection followed by a Corey-Kim oxidation on the alcohol lead to the desired compound **I-27**. The second approach engaged the isocyanide **I-28**, methylhydroxylamine and acetic acid to deliver the macrolactam **I-32**. After β-elimination with released of AcOH, the imine **I-33** underwent spontaneously hydrolysis and transannular cyclization to afford the key product **I-27** (Scheme 7).



Scheme 7: Formation of the tetracyclic skeleton from two isocyanide-based MCR approaches.

The total synthesis of (±)-Trigonolimine B (**I-34**) has also been intensively investigated by our group through isocyanide chemistry. The first retrosynthesis approach envisioned the application of the Ugi-4CR as an initial step. With this proposal only four steps were required for the synthesis of (±)-Trigonolimine B (Scheme 8). However, after numerous experiments on this first step, this retrosynthesis analysis has shown to be unfruitful.[12]



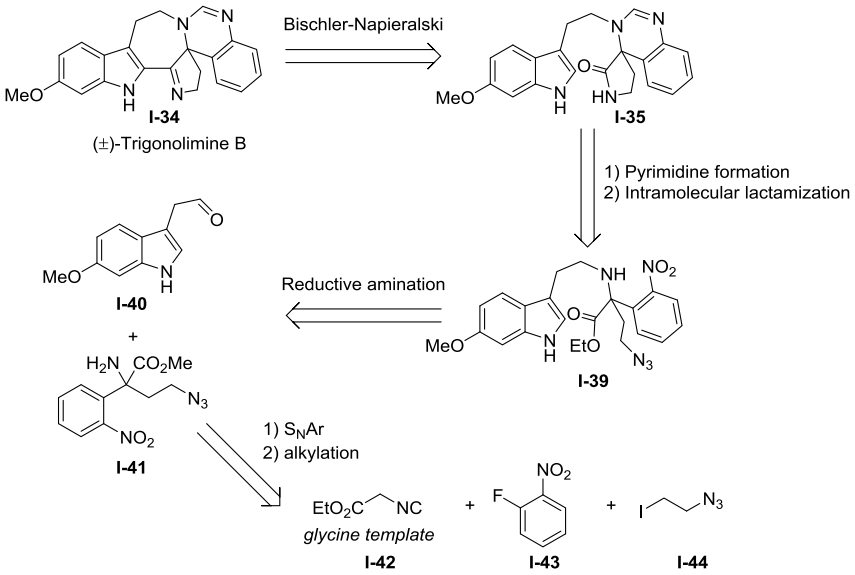
Scheme 8: First unsuccessful retrosynthesis approach: Ugi-4MCR.

…through isocyanoacetate…

To synthesize the challenging quaternary carbon present in the natural product, we decided to use the reactivity of α-isocyanoacetate as alternative. With two electron withdrawing groups on the same carbon, this small molecule possesses strong nucleophilic

[12] T. Buyck, J. Zhu, *Isocyanoacetates as Synthetic Platform Towards Natural Products and Biologically Relevant Scaffolds, PhD Thesis*, **2014**.

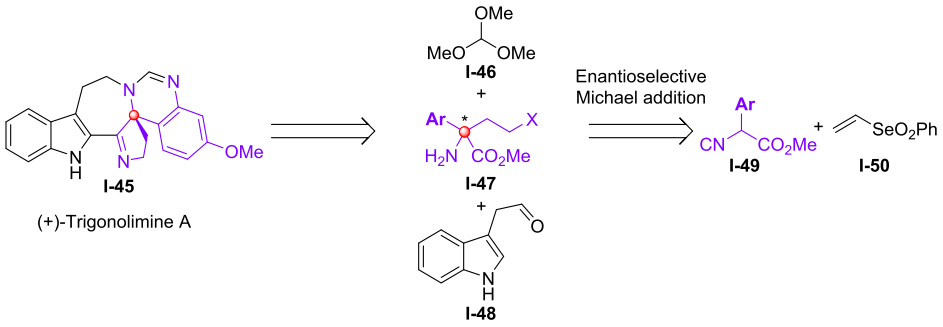
properties. The double functionalization of this camouflaged glycine template has allowed the easy construction of fully substituted carbon. With this approach depicted in Scheme 9, the total synthesis of (±)-Trigonolimine B was accomplished with the Bischler-Napieralski reaction on the spiro compound **I-35** as end-game step. **I-36** was made *via* two ring-closing on compound **I-39**. The indole **I-39** was synthesized from the reductive amination of 2-(6-(methoxy)indol)-acetaldehyde **I-40** and the α,α-disubstituted α-aminoester **I-41**. An aromatic nucleophilic substitution and an alkylation with the α-isocyanoacetate formed the desired compound I-41 which contain the quaternary carbon.[13]



Scheme 9: Our successful retrosynthesis approach for the total synthesis of (±)-Trigonolimine B: α-isocyanoacetate approach.

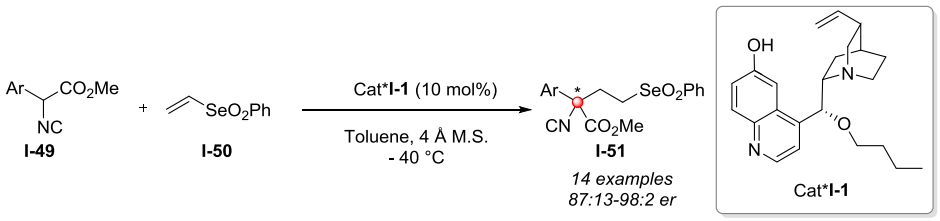
After the racemic 7 steps-total synthesis of (±)-Trigonolimine B, we envisaged the enantioselective synthesis of another member of this indole alkaloid family, Trigonolimine A (**I-45**). The retrosynthetic analysis for the synthesis of (+) or (-)-Trigonolimine A has been very similar to the one previously described (Scheme 10). This natural product could be disconnected to three parts: trimethyl orthoformate **I-46**, a chiral quaternary α-aminoester **I-47** and an aldehyde derivative of tryptamine **I-48**. To install the chiral quaternary carbon of the compound **I-47**, we decided to develop an enantioselective Michael addition of α-aryl α-isocyanoacetate **I-49** to phenyl vinyl selenone **I-50**.[14]

[13] T. Buyck, Q. Wang, J. Zhu, *Org. Lett.* **2012**, *14*, 1338.
[14] T. Buyck, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12714.



Scheme 10: Enantioselective retrosynthesis approach for the total synthesis of Trigonolimine A

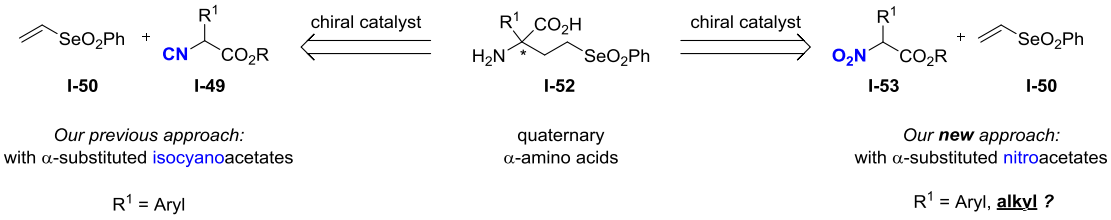
After intensive reaction conditions screening (catalyst, solvent, temperature, additives…), the optimized enantioselective Michael addition of α-substituted α-isocyanoacetate **I-49** and phenyl vinyl selenone occurred smoothly using 10 mol% of *Cinchona* alkaloid as organocatalyst in toluene at -40 °C during 3 days. Good yields and enantioselectivities were obtained and various substituted aromatics (with donating or withdrawing group in *ortho*, *meta* and *para* position) and heterocycles on the α-aryl isocyanoacetate were tolerated (Scheme 11). With this methodology, the synthesis of enantioenriched quaternary α-amino acids derivatives, important building blocks massively used in organic chemistry and biochemistry, has been possible. However, it is important to notice that the scope of the Michael addition was limited. Effectively, when alkyl groups were used as substituent on the α-substituted α-isocyanoacetate, the *Cinchona* alkaloid-catalyzed enantioselective Michael addition was inhibited.



Scheme 11: Enantioselective Michael addition of α-aryl α-isocyanoacetate to phenyl vinyl selenone developed in our group.

…up to nitroacetate

With the hope of overcoming the scope limitation encountered in our previous enantioselective methodology for the synthesis of quaternary amino acids, we decided to change our approach from isocyanide chemistry to other reactive synthetic synthon. The first chapter will focus on the work investigated on α-substituted α-nitroacetate **I-53** as Michael donor in the enantioselective Michael addition with phenyl vinyl selenone **I-50** (Scheme 12).



Scheme 12: From α-isocyanoacetate to α-nitroacetate.

Introduction

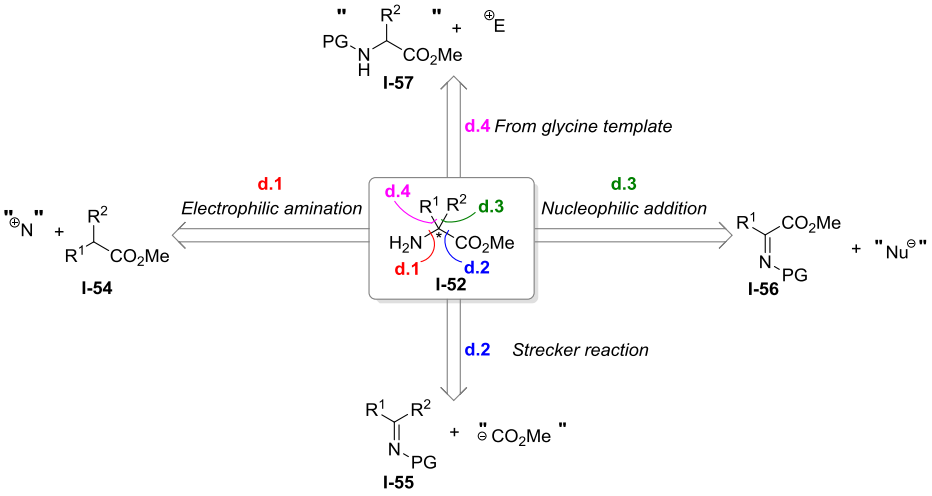
Background on the enantioselective synthesis of quaternary α-amino acid

The interest for the synthesis of quaternary α-amino acids has been growing during the last decades in the biological, biochemical and pharmaceutical fields.[15] Due to the presence of an additional substituent on the α-carbon, the fully substituted amino acid is more persistent *in-vivo* and the racemization of the chiral center is thereby avoided. This tetrasubstituted amino acid, when integrated in a peptide, modified the secondary structure of the proteins which could generate the denial of a problematic enzyme-linked receptor. With this alternative to the twenty well-known natural amino-acids, the fully α-substituted α-amino acids have become relevant building blocks for the synthesis of unnatural and natural compounds and for the design of proteins and peptidomimetics. Therefore, numerous efficient enantioselective syntheses of quaternary α-amino acids have been developed.[16]

Retrosynthetically, different disconnections has been described for the synthesis of quaternary α-amino acids **I-52** (Scheme 13). The first possibility could be the cleavage of the C-N bond; this disconnection would correspond to the electrophilic amination of α,α-disubstituted ester **I-54** to a nitrogen unit (Scheme 13, **d.1**). The second possible could be the C-C bond connected to the ester group, this breaking would match with the Strecker reaction of a cyanide to a ketimine **I-55** (Scheme 13, **d.2**). The third approach could be the carbon-carbon disconnection **d.3**. This bond would be formed *via* nucleophilic addition of nucleophiles to α-ketiminoesters **I-56** (Scheme 13, **d.3**). After breaking **d.4**, the fully substituted α-amino acid could also be synthesized by reacting a glycine template **I-57** which would play the role of nucleophile on an electrophilic specie (Scheme 13, **d.4**).

[15] (a) S. Omura, T. Fujimoto, K. Otaguro, K. Matsuaki, R. Moriguchi, H. Tanaka, Y. Sasaki, *J. Antibiot.* **1991**, *44*, 113; (b) S. Omura, K. Matsuzaki, T. Fujimoto, K. Kosuge, T. Furuya, S. Fujita, A. Nakagawa, *J. Antibiot.* **1991**, *44*, 117; (c) G. Fenteany, R. G. Standaert, W. S. Lane, S. Choi, E. J. Corey, S. L. Schreiber, *Science* **1995**, *268*, 726; (d) J. A. Monn, M. J. Valli, S. M. Massey, R. A. Wright, C. R. Salhoff, B. G. Johnson, T. Howe, C. A. Alt, G. A. Rhodes, R. L. Robey, K. R. Griffey, J. P. Tizzano, M. J. Kallman, D. R. Helton, D. D. Schoepp, *J. Med. Chem.* **1997**, *40*, 528.

[16] Reviews on the synthesis of quaternary α-amino acids: (a) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9* 3517; (b) Y. Ohfune, T. Shinada, *Eur. J. Org. Chem.* **2005**, *24*, 5127 ; (c) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **2007**, *18*, 569 ; (d) H. Vogt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406; (e) R. A. Mosey, J. S. Fisk, J. J. Tepe, *Tetrahedron: Asymmetry* **2008**,*19*, 2755; (f) C. Cativiela, M. Ordóñez, *Tetrahedron: Asymmetry* **2009,** *20*, 1 ; (g) K. Bera, I. N. N. Namboothiri, *Asian J, Org Chem.* **2014**, *3*, 1234 (h) A. E. Metz, M. C. Kozlowski, *J. Org. Chem.* **2015**, *80*, 1.

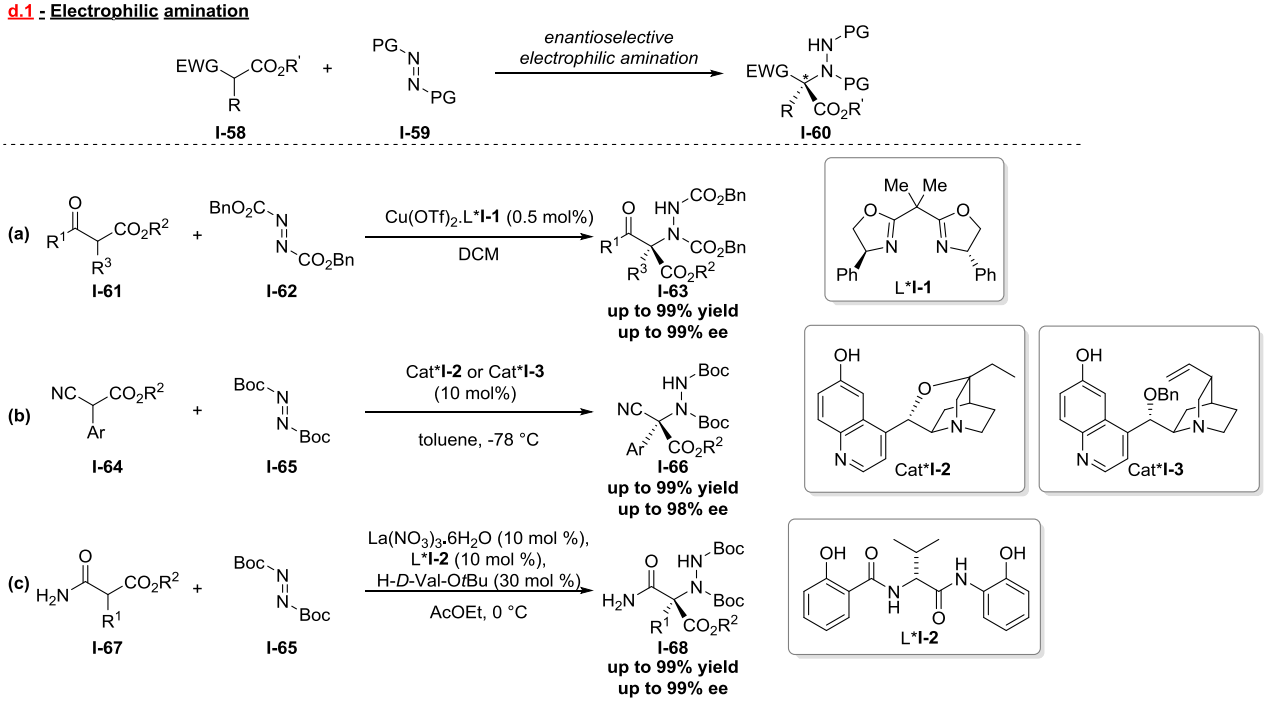


Scheme 13: Possible disconnection for the synthesis of enantoenriched quaternary α-amino acid

1- Enantioselective electrophilic amination – (disconnection d.1)

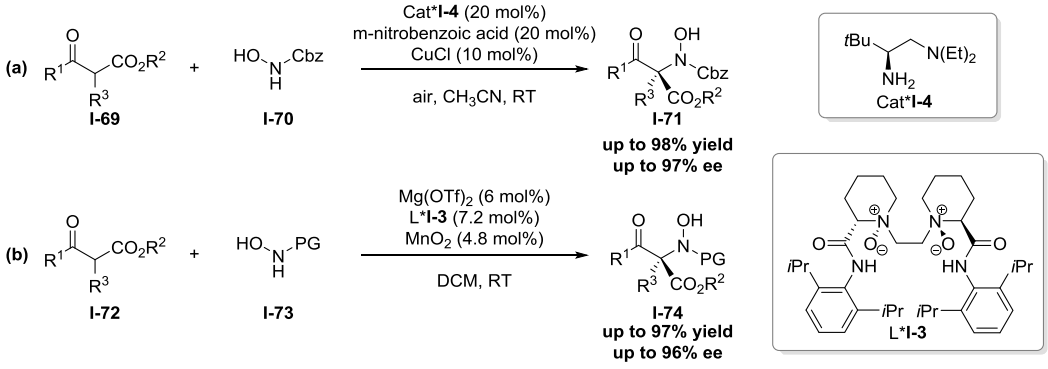
Generally introduced by the addition of an amine on an electrophile, the nitrogen unit has been also incorporated via the less conventional electrophilic amination. In 2003, Jørgensen described an enantioselective synthesis of quaternary α-amino acid by a $Cu(OTf)_2$/Box ligand-catalyzed reaction of β-ketoester **I-61** and dibenzyl azodicarboxylate **I-62** (Scheme 14 **(a)**).[17a] Organocatalysis induced also this asymmetric transformation and *cinchona* alkaloids have been described to give high yields and enantioselectivities when α-substituted α-cyanoacetate **I-64** and azodicyarboxylate **I-65** reacted together (Scheme 14 **(b)**).[17b] Primary α-alkoxycarbonyl amides **I-67** and azodicarboxylate **I-65** with lanthanum-based ternary catalyst described by Shibazaki offered also highly enantioenriched fully substituted α-amino acids in good yields (Scheme 14 **(c)**).[17c]

[17] With azadicarboxylate (a) M. Marigo, K. Juhl, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 1367; (b) S. Saaby, M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 8120; (c) T. Mashiko, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 14990.



Scheme 14: Enantioselective electrophilic amination with azadicarboxylate.

N-hydroxycarbamate has been another suitable electrophilic nitrogen donor. In 2014, the group of Luo reported the unprecedented asymmetric organocatalytic α-amination of α-substitued β-ketoester **I-69** with *N*-hydroxycarbamate **I-70** (Scheme 15, **(a)**).[18a] The same year, Yamamoto and coworkers described the Lewis acid-catalyzed asymmetric hydroxyamination of α-substituted β-ketoester **I-72** (Scheme 15, **(b)**). In these two reports, the *N*-hydroxycarbamate **I-73** was converted *in situ* to a reactive nitroso species which was mandatory for the electrophilic α-amination.[18b]



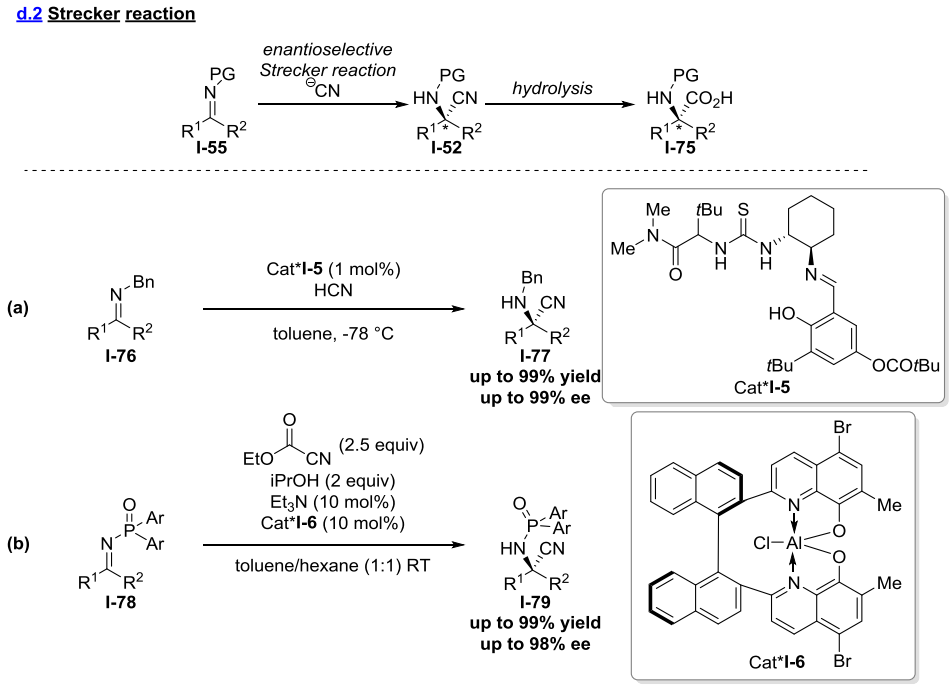
Scheme 15: Enantioselective electrophilic amination with *N*-hydroxycarbamate.

[18] With N-hydroxycarbamate (a) C. Xu, L. Zhang, S. Luo, *Angew. Chem. Int. Ed.* **2014**, *53*, 4149; (b) B. Maji, M. Baidya, H. Yamamoto, *Chem. Sci.* **2014**, *5*, 3941.

2- Enantioselective Strecker reaction - (disconnection d.2)

Several cyanation reactions have been developed but it has been the Strecker reaction which was the mostly studied.[19] This 3-component reaction involving a carbonyl, an amine and a cyanide was originally developed in 1850 by Adolph Strecker when acetaldehyde, ammonia and hydrogen cyanide were mixed together to deliver α-substituted α-cyanoamine.[20] The subsequent hydrolysis of the nitrile group permited the formation of the desirable α-amino acid.

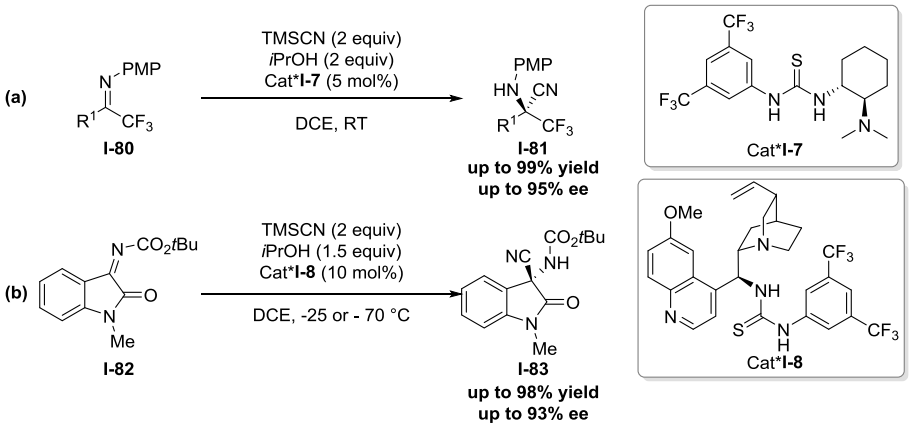
The use of ketimines with cyanide for the asymmetric synthesis of quaternary α-amino acid has been preliminarily reported by Jacobsen. Reaction of HCN with *N*-benzyl protected ketimine in the presence of a thiourea as organocatalyst at -78 °C in toluene, the α,α-disubstituted α-cyanoamines **I-76** were obtained in excellent yield and enantioselectivity (Scheme 16 **(a)**).[21a] In 2009, Yamamoto reported the use of cyanoformate as cyanide source in the enantioselective addition of cyanide to ketimine with an aluminium complex Cat***I-6** as Lewis acid catalyst. This less toxic and less volatile cyanide source has been a good alternative and easier-to-handle reagent (Scheme 16 **(b)**).[21b]



Scheme 16: Enantioselective Strecker reaction.

[19] Review on catalytic asymmetric cyanation reactions : N. Kurono, T. Ohkuma, *ACS Catal.* **2016**, *6*, 989.
[20] A., Strecker *Ann. Chem. Pharm.* **1850**, *75*, 27.
[21] First Strecker reaction with ketimine: P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867; P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012; (b) ethyl cyanoformate as cyanide source J. P. Abell, H. Yamamoto, *J. Am. Chem. Soc.* **2009**, *131*, 15118.

The enantioselective cyanation of other substrates such as α-trifluoromethyl ketimine **I-80** or isatin ketimine **I-82** derivative has also been described with the Strecker reaction using TMSCN and the adapted organocatalyst (Scheme 17, **(a)** & **(b)**).[22]

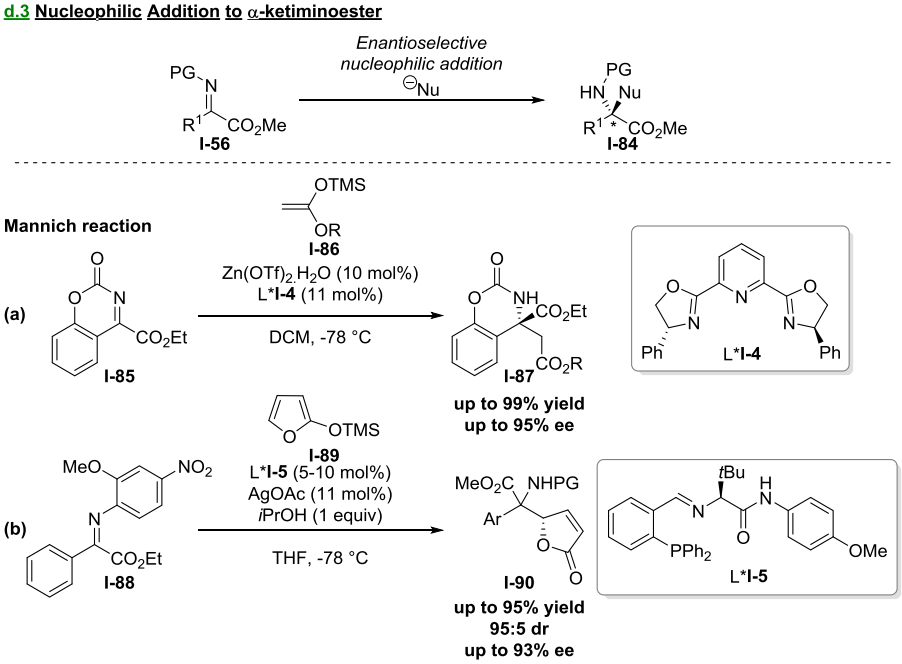


Scheme 17: Enantioselective Strecker reaction with other substrates.

3- α-Ketiminoester for enantioselective synthesis of quaternary α-amino acid - (disconnection d.3)

α-Ketiminoesters **I-56** have been used in different enantioselective nucleophilic addition.[23] Asymmetric Mannich reaction, enantioselective alkylation, allylation or alkynylation have been developed for the elaboration of quaternary amino acids. In 2003, Jørgensen and coworkers reported the first enantioselective Mannich reaction with cyclic ketimine **I-85**, silyl ketene acetal **I-86** and zinc-(Py)box L***I-4** as chiral complex. This methodology allowed the formation of tetrasubstituted amino acid with yield up to 99% and 95% enantioselective excess (Scheme 18 **(a)**).[24a] Vinylogous Mannich reaction has also been described by Hoveyda. This diastereo and enantioselective Ag-catalyzed reaction of α-ketiminoesters **I-88**, a commercially available siloxyfuran **I-89**, silver acetate and a chiral ligand L***I-5** offered quaternary amino acids where two asymmetric contiguous stereocenters have been created (Scheme 18 **(b)**).[24b]

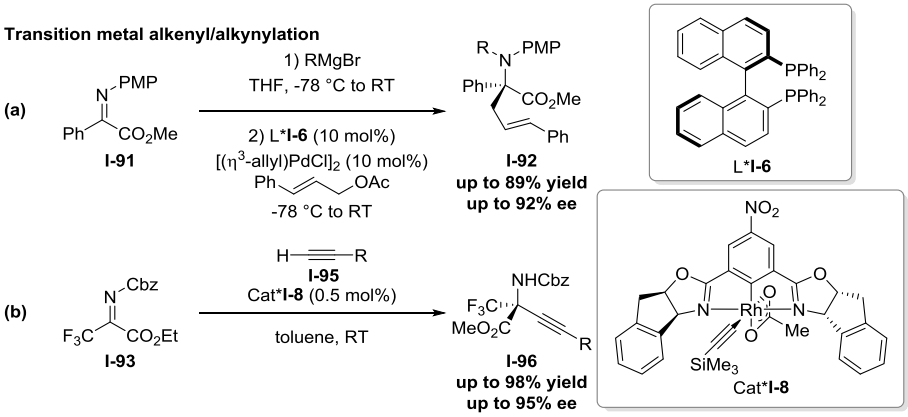
[22] (a) α-CF_3 ketimine as substrate D. Enders, K. Gottfried, G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 3147; (b) isatin as substrate D. Wang, J. Liang, J. Feng, K. Wang, Q. Sun, L. Zhao, D. Li, W. Yan, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 548; Y.-L. Liu, J. Zhou, *Chem. Commun.* **2013**, *49*, 4421.
[23] Review on α-ketiminoester B. Eftekhari-Sis, M. Zirak, *Chem. Rev.* **2017**, *117*, 8326.
[24] (a) S. Saaby, K. Nakama, M. A. Lie, R. G. Hazell, K. A. Jørgensen *Chem. Eur. J.* **2003**, *9*, 6145 (b) L. C. Wieland, E. M. Vieira, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.*, **2009**, *131*, 570.



Scheme 18: Enantioselective Mannich reaction with α-ketiminoester.

Transition metal-catalyzed reactions with α-ketiminoesters have been another approach for the synthesis of tetrasubstituted quaternary amino acids. In 2014, Kozlowski developed the enantioselective 3-CR reaction between α-iminoesters **I-91**, Grignard reagents, and cinnamyl acetate. Using the umpolung *N*-addition on α-iminoesters developed by Kagan and Fiaud;[25] the alkyl Grignard attacked first the nitrogen of the ketimine to generate a stabilized enamine intermediate. After, this intermediate reacted with the palladium π–allyl electrophile to afford α-allyl-α-aryl-α-amino acids **I-92** (Scheme 19, **(a)**).[26a] Recently, Ohshima *et al* have described enantioselective alkynylation of α-ketiminoester **I-93** with terminal alkynes **I-95** and adaptable rhodium (III) complexes as chiral catalyst. It was notable that this transformation using (trimethylsilylethynyl)rhodium(III) as precatalyst with a loading of 0.5 mol% could accomplish the formation of highly enantioenriched quaternary amino acids in good yield (Scheme 19, **(b)**).[26b]

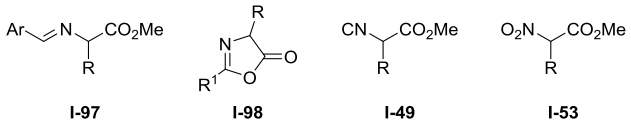
[25] Fiaud, J. C.; Kagan, H. *Tetrahedron Lett.* **1970**, *11*, 1813.
[26] (a) J. M. Curto, J. S. Dickstein, S. Berritt, N. C. Kozlowski, *Org. Lett.* **2014**, *16*, 1948; (b) K. Morisaki, M. Sawa, R. Yonesaki, H. Morimoto, K. Mashima, T. Ohshima, *J. Am. Chem. Soc.* **2016**, *138*, 6194.



Scheme 19: Enantioselective metal-catalyzed transformations with α-ketiminoester.

4- Glycine templates for enantioselective synthesis of quaternary α-amino acid - (disconnection d.4)

Among the possible manner of synthesizing quaternary α-amino acids, the use of glycine template has been intensively investigated (Scheme 20). α-substituted (arylideneamino)acetate **I-97**,[27] oxazolones **I-98**,[28] α-substituted α-isocyanoacetates **I-49** [29] and α-substituted α-nitroacetates **I-53** have shown to be good glycine masks for the development of enantioenriched reaction. As many asymmetric alkylation, allylation and Michael addition have been reported over the year for the synthesis of highly enantioenriched tetrasubstituted α-amino acid with the different glycine templates, we have chosen to describe only the literature background of α-substituted nitroacetate for the synthesis of enantioenriched quaterny α-amino acids.



Scheme 20: Glycine template used for the synthesis of enantioenriched quaternary α-amino acids .

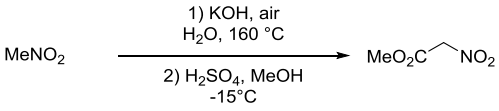
α-nitroacetate as privileged partner

Synthesis of nitroacetate derivative

α-Nitroacetate is a small molecule enormously studied by the chemistry community. The easy modification of the functional groups[30] and the high acidity of the α proton[31] has

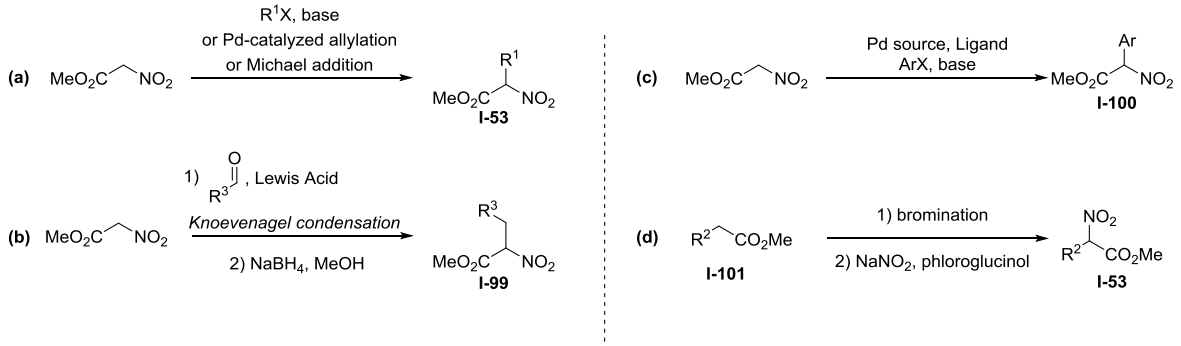
[27] (Arylideneamino)acetate: T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.
[28] Oxazolone: A.-N. R. Alba, R. Rios, *Chem. Asian J.* **2011**, *6*, 720.
[29] α-Isocyanoacetates (a) Y. Ito, M. Sawamura, M. Matsuoka, Y. Matsumoto, T. Hayashi *Tetrahedron Lett.* **1987**, *28*, 4849; J.-F. Bai, L.-L. Wang, L. Peng, Y.-L. Guo, L.-N. Jia, F. Tian, G.-Y. He, X.-Y. Xu, L.-X. Wang, *J. Org. Chem.* **2012**, *77*, 2947.
[30] N. Ono, *The Nitro Group in Organic Synthesis Wiley-VCH*, **2001**, 159.

given to this glycine template attractive properties for the development of new synthetic transformation. Steinkopf was the first to isolate alkyl α-nitroacetate in moderate yield by adding carefully nitromethane in a saturated aqueous solution of potassium hydroxide under air atmosphere at reflux.[32] Esterification of the subsequent dipotassium salt using sulfuric acid in methanol offered the desired methyl nitroacetate. It was noteworthy that this reaction was reproducible and has been optimized to the mole scale.[32c]



Scheme 21: α-Nitroacetate synthesis

α-Substituted α-nitroacetate, derivative of α-nitroacetate needed for the enantioselective synthesis of quaternary α-amino acid, could be synthesized by alkylation, Pd-catalyzed allylation or Michael addition (Scheme 22 **(a)**).[33] To avoid the double alkylation which was competing in some cases with the mono alkylation, the Knoevenagel condensation of aldehyde with α-nitroacetate has been a good alternative. (Scheme 22 **(b)**).[34] It was also possible to synthesize α-aryl α-nitroacetate **I-100** with a direct palladium-catalyzed arylation of α-nitroacetate developed by Kozlowski in 2012.[31] Finally the simple α-bromination of alkyl ester **I-101** followed by a S_N2 reaction to introduce the nitro group using sodium nitrite has permited the access to various α-alkyl α-nitroacetate.[35]



Scheme 22: α-Substituted α-nitroacetates syntheses.

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[31] pKa of nitroacetate described as 5.8 in: A. E. Metz, S. Berritt, S. D. Dreher, M. C. Kozlowski, *Org. Lett.*, **2012**, *14*, 760.

[32] (a) W. Steinkopf, *Ber. Dtsch. Chem. Ges.* **1909** *42*, 3925; (b) for more deatil on the history of nitroacetate synthesis, see: D. A. Lyttle, D. I. Weisblat, *J. Am. Chem. Soc.* **1947**, *69*, 2118; (c) one mole scale protocole: S. Zen, M. Koyama, S. Koto, *Org. Synth.* **1976**, *55*, 77.

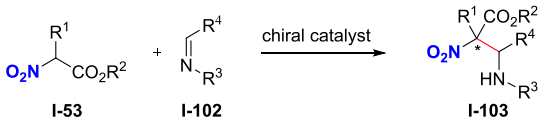
[33] Allylation J.P. Genet, D. Ferround *Tetrahedron. Lett.* **1984**, *25*, 3579; alkylation N. Kornblum, R. K. Blackwood, *Org. Synth.* **1988**, *57*, 60; Michael addition E. Trogu, F. De Sarlo, F. Machetti, *Chem. Eur. J.* **2009**, *15*, 7940.

[34] Knoevenagel : S. Nakamura, M Uchiyama, T. Ohwada, *J . Am. Chem. Soc.* **2003**, *125*, 5282.

[35] N. Kornblum, R. K. Blackwood, *Org. Synth.* **1957**, *37*, 44.

Enantioselective transformation with α-substituted α-nitroacetate

Over the years, different asymmetric methods have been developed for the enantioselective synthesis of α,α-disubstituted nitroacetates. One of the most established approach have been the nitro Mannich (or aza-Henry) reaction. This reaction involved the nucleophilic addition of α-substituted nitroacetate **I-53** to the protected imine **I-102** leading to the corresponding α-nitro α-aminoester **I-103**. Chiral catalysts or chiral ligand were the key for the stereocontrol of the chiral center (Scheme 23).

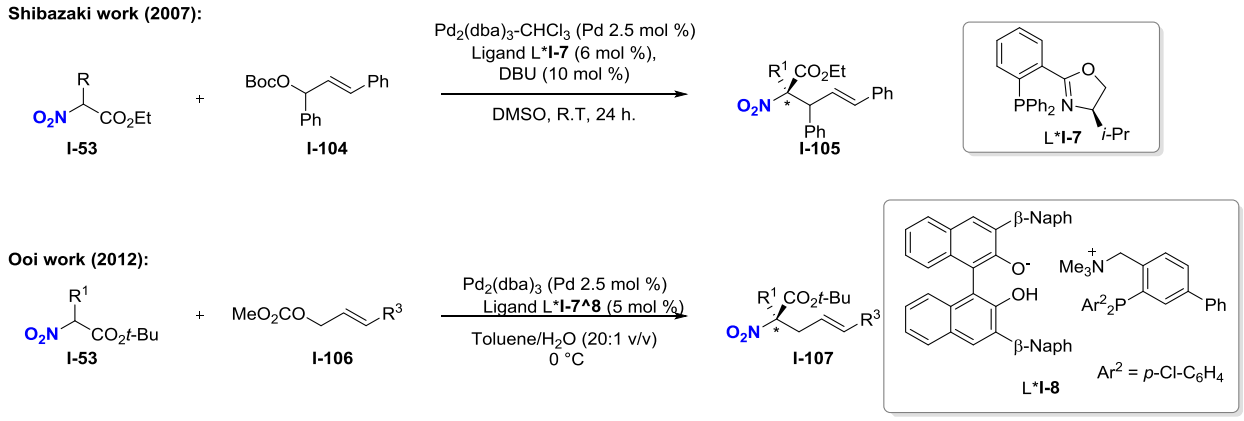


Scheme 23: Enantioselective nitro Mannich reaction for the synthesis of α-nitro α-amino ester.

Jørgensen and coworkers reported in 2005 the catalytic enantioselective nitro Mannich reaction using α-substituted nitroacetates as nucleophiles.[36] In the presence of $Cu(OTf)_2$ as Lewis acid, (*R*)-Ph-Box as chiral ligand and quinine as Brønsted base, the formation of α-nitro α-amino ester **I-103** was done in 98% yield with a *dr* of 14:1 and an *ee* of 75%.

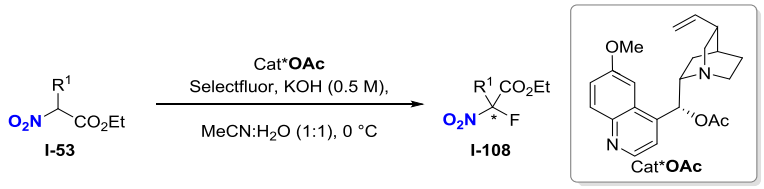
Another way of α,α-disubstituted nitroacetate synthesis was the asymmetric allylic alkylation of α-substituted nitroacetate **I-53** with allylic carbonate **I-104**. This method was highlighted by Shibasaki *et al.* in 2007 and Ooi *et al.* in 2012 (Scheme 24).[37] To perform this asymmetric transformation for the construction of α,α-disubstitued nitroacetates **I-105** and **I-107**, chiral ligand such as phosphinooxazoline L***I-7** or the ammonium-phosphine ion pair ligand L***I-8** were needed.

[36] K. R. Knudsen, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 1362.
[37] (a) K. Maki, M. Kanai, M. Shibasaki, *Tetrahedron*, **2007**, *63*, 4250; (b) K. Ohmatsu, M. Ito, T. Kunieda, T. Ooi, *Nat. Chem.* **2012**, *4*, 473.



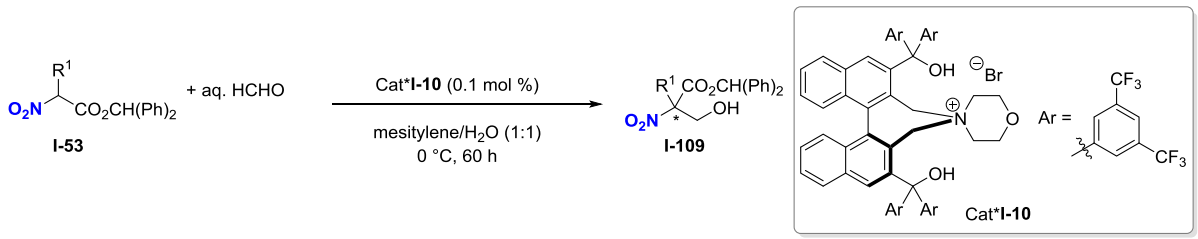
Scheme 24: Enantioselective allylic alkylation of α-substituted nitroacetate.

In 2007, Togni and coworkers designed the synthesis of α-fluoro α-substituted nitroacetate **I-108** by the asymmetric electrophilic fluorination of α-substituted nitroacetate **I-53** (Scheme 25).[38] The fluorinating reagent was made *in situ* by combining a *Cinchona* alkaloid derivative and Selectfluor. However, the best result was obtained using acetylquinine as organocatalyst to give product in 98% yield and only 40% *ee*.



Scheme 25: α-Fluorination of α-substituted nitroacetate.

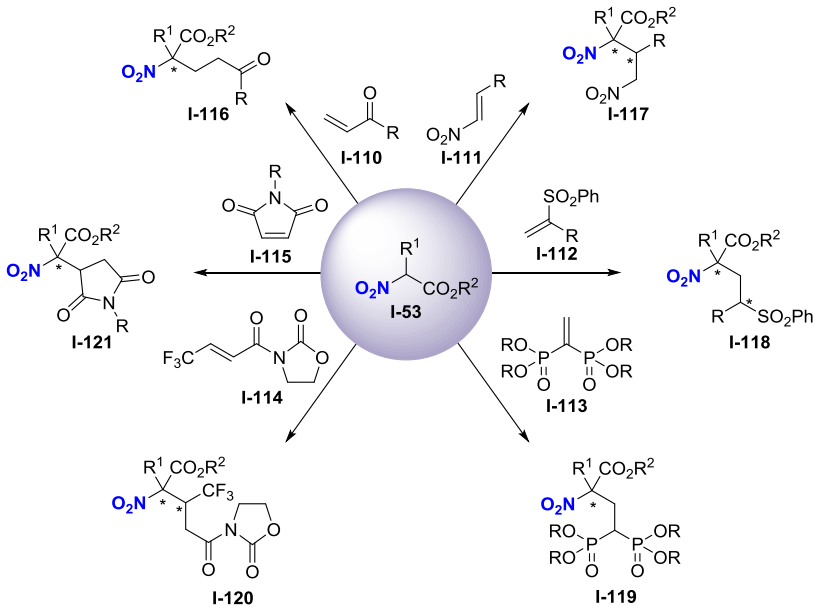
More recently, Maruoka's group reported the catalytic asymmetric aldol reaction of α-substituted nitroacetate **I-53** with aqueous formaldehyde (Scheme 26).[39] This reaction was performed with a bifunctional chiral phase-transfer catalyst Cat***I-10** which allowed the formation of α-alkyl serine derivatives **I-109**.



Scheme 26: Catalytic asymmetric aldol reaction of α-substituted nitroacetate to aqueous formaldehyde.

[38] J. Ramírez, D. P. Huber, A. Togni, *Synlett*, **2007**, 1143.
[39] S. Shirakawa, K. Ota, S. J. Terao, K. Maruoka, *Org. Biomol. Chem.* **2012**, *10*, 5753.

The asymmetric conjugated addition of α-substituted nitroacetate **I-53** to various Michael acceptors has been also a good method for the synthesis of quaternary amino acid derivatives.[40] α,α-unsaturated ketones **I-110** [41], nitro olefins **I-111**,[42] α,β-unsaturated sulfones **I-112**,[43] ethylidenebisphosphonate **I-113**,[44] α-trifluoromethylated acrylamide **I-114**,[45] or maleimide **I-115**[46] were used as Michael acceptors (Scheme 27). Different organocatalysts were used to perform these transformations in good enantioselectivity.



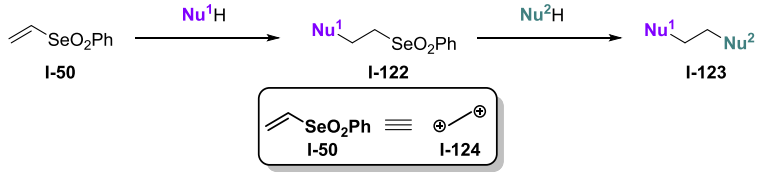
Scheme 27: Michael addition of α-substituted nitroacetate to various Michael acceptor partners.

The asymmetric conjugated addition of α-substituted nitroacetate **I-53** has permited the formation of a wide range of quaternary α-amino acid derivatives (**I-116** to **I-121**). But some interesting Michael acceptors have still not been investigated with α-substituted α-nitroacetate, such as phenyl vinyl selenone.

[40] R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *3*, 933.
[41] (a) E. Keller, N. Veldman, A. L. Spek, B. L. Feringa, *Tetrahedron: Asymmetry*, **1997**, *20*, 3403; (b) J. R. Duvall, F. Wu, B. B. Snider, *J. Org. Chem.* **2006**, *71*, 8579; (c) B. R. Linton, M. H. Reutershan, C. M. Aderman, E. A. Richardson, K. R. Brownell, C. W. Ashley, C. A. Evans, S. J. Miller, *Tetrahedron Lett.* **2007**, *48*, 1993.
[42] (a) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem. Int. Ed.* **2005**, *44*, 105; (b) X.-Q. Dong, H.-L. Teng, C.-J. Wang, *Org. Lett.* **2009**, *6*, 1265; (c) Y.-Z. Li, F. Li, P. Tian, Guo.-Q. Lin, *Eur. J. Org. Chem.* **2013**, *8*, 1558.
[43] A. Quintard, A. Alexakis, *Org. Biomol. Chem.* **2011**, *9*, 1407.
[44] Y. Kato, Z. Chen, S. Matsunaga, M. Shibasaki, *Synlett* **2009**, *10*, 1635.
[45] L Wen, L. Yin, Q. Shem, L. Lu., *ACS Catal.* **2013**, *3*, 502.
[46] S. Shirakawa, S. J. Terao, R. He, K. Maruoka, *Chem. Commun.*, **2011**, *47*, 10557.

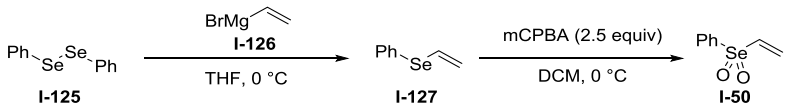
Reactivity and synthesis of phenyl vinyl selenone

Phenyl vinyl selenone (**I-50**) is a small molecule where the phenyl selenonyl group acts as electron-withdrawing group and leaving group. With this double ability, the organic compound can play firstly the role of Michael acceptor with one nucleophile. A second nucleophile can be incorporated with displacement of the -SeO_2Ph group which permits the rapid formation of complex molecules and the development of numerous domino processes. Synthetically, the phenyl vinyl selenone can be considered as an ethane dication moiety **I-124** (Scheme 28).



Scheme 28: Phenyl vinyl selenone reactivity.

The synthesis of phenyl vinyl selenone could be achieved in two steps from diphenyl diselenide **I-125** using a Grignard reaction with vinyl magnesium bromide **I-126** as first step. After the double oxidation of the subsequent selenide **I-127** with *m*-CPBA, the phenyl vinyl selenone **I-150** could be isolated in 80% yield.

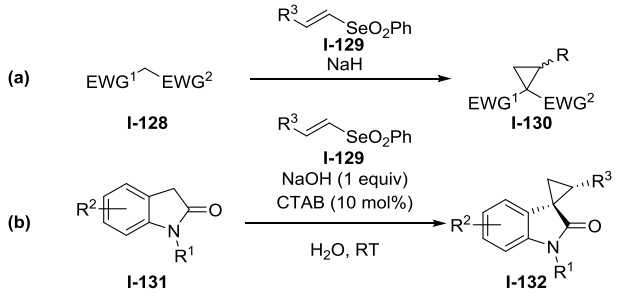


Scheme 29: Phenyl vinyl selenone synthesis.

Cyclopropane synthesis

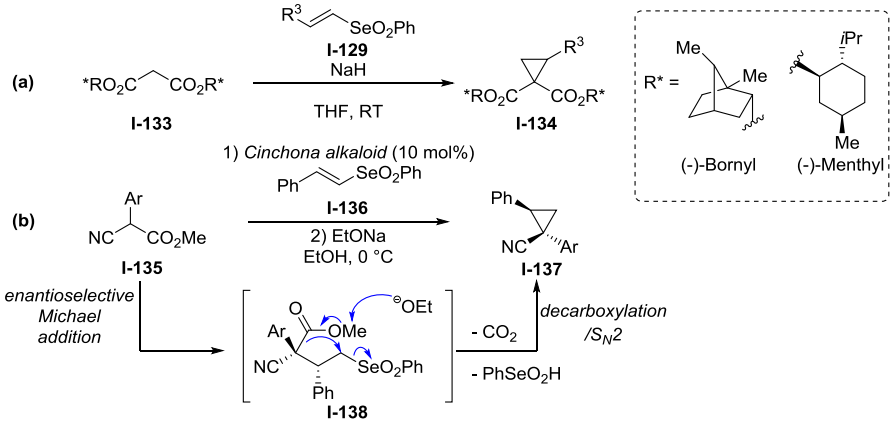
Due to this dicationic reactivity pattern, vinyl selenone has been used for the cyclopropanation of malonate derivative. Dialkyl malonate, β-ketoester, β-ketoamide, α-cyanoacetate or nitromethane could act as double nucleophile on phenyl vinyl selenone when sodium hydride was used (Scheme 30, **(a)**).[47a] Oxindole derivatives **I-131** have also been used with vinyl selenone in basic aqueous medium to form spiro compounds **I-132** (Scheme 30 **(b)**).[47b]

[47] Cyclopropanation (a) I. Kuwajima, R. Ando, T. Sugawara, *Tetrahedron Lett.* **1983**, *24*, 4429; R. Ando, T. Sugawara, M. Shimizu, I. Kuwajima, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2897; M. Tiecco, D. Chianelli, L. Testaferri, M. Tingoli, D. Bartoli *Tetrahedron* **1986**, *42*, 4889; (b) M. Palomba, L. Rossi, L. Sancineto, E. Tramontano, A. Corona, L. Bagnoli, C. Santi, C. Pannecouque, O. Tabarrini, F. Marini, *Org. Biomol. Chem.* **2016**, *14*, 2015.



Scheme 30: Cyclopropanation with phenyl vinyl selenone.

A first trial of the diastereoselective cyclopropanation using chiral auxiliary, (-)-dibornyl or (-)-dimenthyl malonate, has been explored by Tiecco and Bagnoli (Scheme 31 **(a)**). [48a] Unfortunately, low diastereoselectivity was observed with the chiral malonates **I-133**. It was still possible to separate by column chromatography the diastereoisomers which, after removal of the bornyl or menthyl groups, allowed the isolation of highly enantioenriched cyclopropanes. Marini and Tiecco reported also the asymmetric cyclopropanation of α-aryl α-cyanoacetate **I-135** with phenyl styryl selenone **I-136**. After a *cinchona* alkaloid-catalyzed Michael addition of the nucleophile **I-135** to the styryl selenone **I-136**, Michael adducts **I-138** were obtained in good yield and moderate enantioselectivity. When treated with sodium ethanoate, a decarboxylation/S_N2 sequence occured on intermediate **I-138** to afford the cyclopropane **I-137** with a complete conservation of the diastereoselectivity and a little erosion of the enantioselectivity (Scheme 31 **(b)**) [48b]



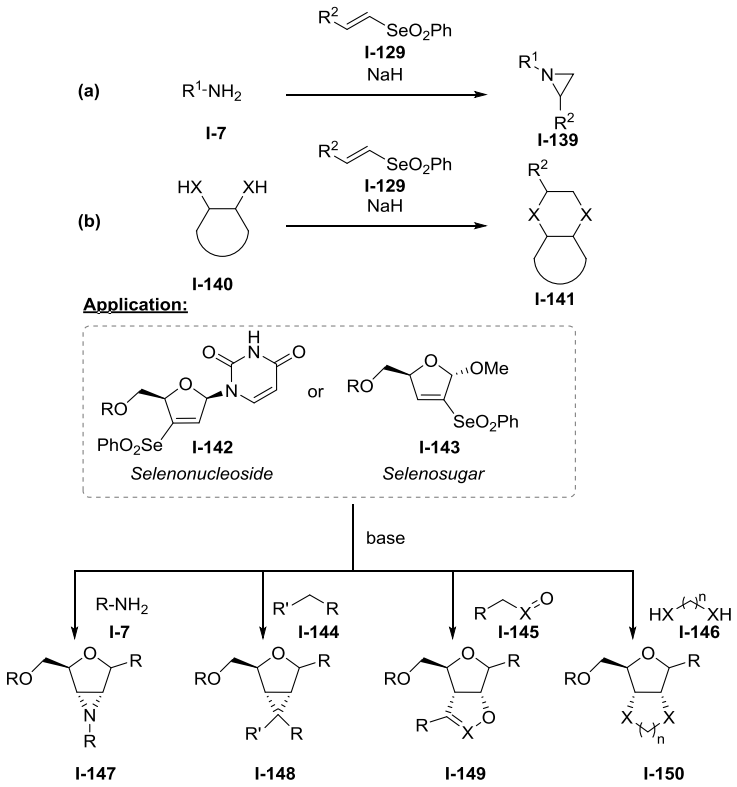
Scheme 31: Trial of disastereoselective cyclopropanation with vinyl selenone.

Double nucleophilic addition

The double nucleophilic addition of heteroatom on phenyl vinyl selenone was also possible. For example, when primary amines **I-7** were mixed with phenyl vinyl selenone, the smooth formation of aziridine **I-139** was occurring (Scheme 32 **(a)**). Chiral amino alcohol,

[48] (a) L. Bagnoli, C. Scarponi, L. Testaferri, M. Tiecco, *Tetrahedron: Asymmetry* **2009**, *20*, 1506; (b) F. Marini, S. Sterativo, F. Del Verme, L. Testaferri, M. Tiecco, *Adv. Synth. Catal.* **2009**, *351*, 1801.

diol and diamine could be used with phenyl alkenyl selenone **I-129** for the synthesis of non-aromatic heterocycles **I-141** (Scheme 32 **(b)**).[49] This chemistry has been applied on nucleoside and sugar selenonyl derivatives (**I-142** & **I-143**) and different modifications of these biomolecules have been described.[50]



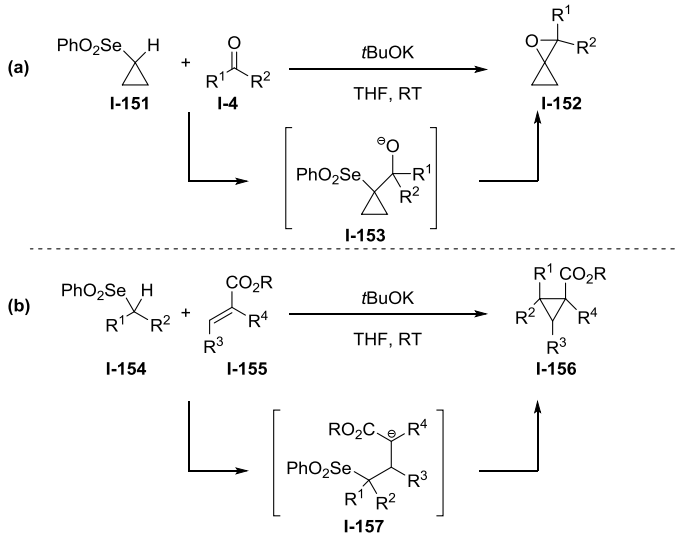
Scheme 32: Heterocycle synthesis using vinyl selenone.

With the electron-withdrawing ability of the phenylselenonyl group, the carbon Cα could be deprotonized. Different reactions have been developed by Krief in 1988 where the α-deprotonation followed by a S_N2 reaction was occurring. The reaction of cyclopropyl phenyl selenone **I-151** with a carbonyl and *t*BuOK as base afforded 1-oxaspiro[2.2]pentane derivative **I-152** (Scheme 34 **(a)**). The Michael addition of the α-deprotonated alkyl phenyl selenone **I-154** on the methyl acrylate **I-155** permited the formation of cyclopropyl ester compounds **I-156** using a similar sequence (Scheme 34 **(b)**).[51]

[49] (a) With primary amine: S. Sternativo, F. Marini, F. Del Verme, A. Calandriello, L. Testaferri, M. Tiecco, *Tetrahedron* **2010**, *66*, 6851; (b) with two heteroatoms: L. Bagnoli, C. Scarponi, M. G. Rossi, L. Testaferri M. Tiecco, *Chem. Eur. J.* **2011**, *17*, 993; L. Bagnoli, S. Casini, F. Marini, C. Santi, L. Testaferri, *Tetrahedron* **2013**, *69*, 481.

[50] Application to selenonuleoside: J. C. Wu, J. Chattopadhyaya, *Tetrahedron* **1989**, *45*, 4507; W. Jin-Chang, J. Chattopadhyaya, *Tetrahedron* **1990**, *46*, 2587; W. Tong, J. C. Wu, A. Sandström, J. Chattopadhyaya, *Tetrahedron* **1990**, *46*, 3037; W. Tong, Z. Xi, C. Gioeli, J. Chattopadhyaya, *Tetrahedron* **1991**, *47*, 3431; application to selenosugar: A. Bhaumik, T. Pathak *J. Org. Chem.* **2015**, *80*, 11057.

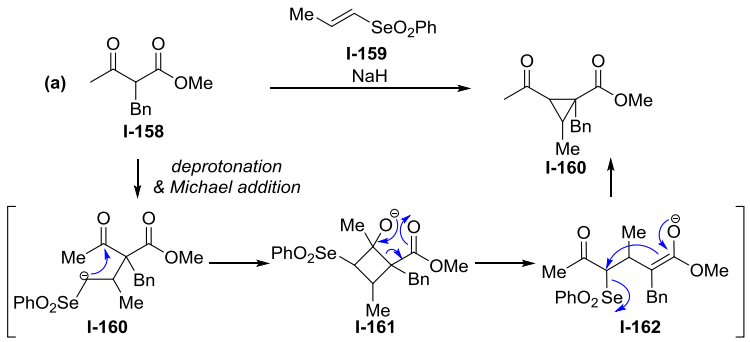
[51] α-Deprotonation: (a) A. Krief, W. Dumont, J. L. Laboureur, *Tetrahedron Lett.* **1988**, *29*, 3265; (b) A. Krief, W. Dumont, A. F. De Mahieu, *Tetrahedron Lett.* **1988**, *29*, 3269.



Scheme 33: α-Deprotonation of alkyl phenyl selenone.

Rearrangement

Different rearrangements have been reported using phenyl vinyl selenone. Kuwajima reported in 1983, the Michael addition of α-benzyl β-ketoester **I-158** with alkenyl phenyl selenone **I-159**. Due to the absence of a second acidic α-proton on the substrate, the resulting negative charge was suggested to attack intramolecularly the ketone to afford the cyclobutane intermediate **I-161**. The alkoxy of the intermediate **I-161** was converted to the ketone with the opening of the 4-membered ring to give the linear enolate **I-162**. After S_N2 of the enolate to display the phenyl selenonyl group, 2-acetylcyclopropane-1-carboxylates **I-160** could be isolated in moderate yield (Scheme 34).[52]



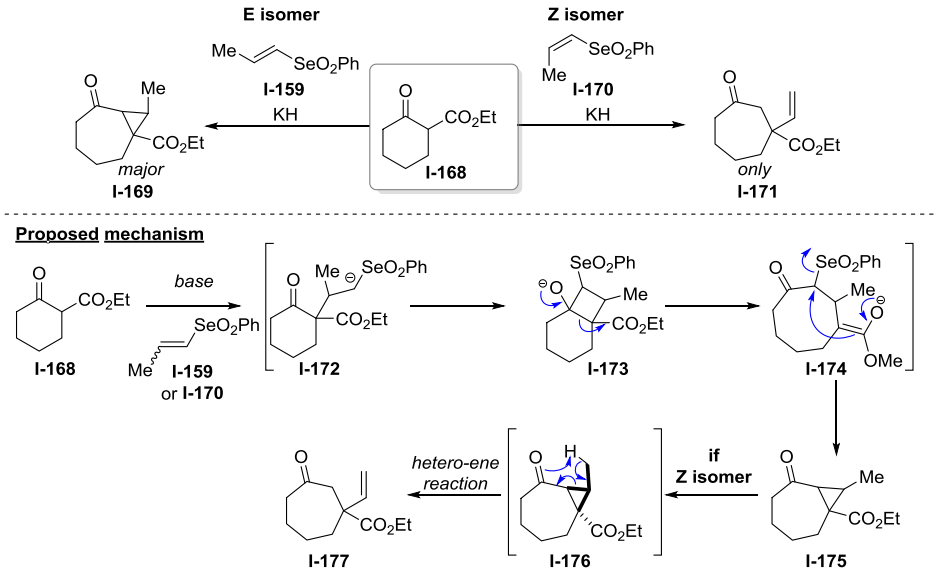
Scheme 34: Rearrangement with β-ketoester and phenyl vinyl selenone.

Ring expansion

A really nice ring expansion of cyclic compound using alkenyl phenyl selenone has been noticed by Kuwajima in 1985. Ethyl cyclohexanone-2-carboxylate **I-168**, when reacted with the *Z* isomer of phenyl prop-1-ene selenone **I-170**, offered the 7-membered ring **I-171**

[52] R. Ando, T. Sugawara, I. Kuwajima, *J. Chem. Soc., Chem. Commun.* **1983**, 0, 1514.

bearing vinyl group. Interestingly, when this alkenyl selenone was replaced by (*E*)-prop-1-ene phenyl selenone **I-159**, the bicyclo[5.1.0]octanone **I-169** was formed. The proposed mechanism to rationalize the two structures started with the Michael addition which afforded the adduct **I-172**. After cyclization to form the 4-membered ring of the compound **I-173**, a ring opening was occurring to deliver **I-161**. Then, the bicyclic molecule **I-175** was obtained after S_N2 of the enolate **I-174** to the phenyl selenonyl group. In the case of *Z*-isomer the conformation of the bicyclic structure allowed the intramolecular hetero-ene reaction of the ketone with the methyl cyclopropane to give the vinyl compound **I-177**.[53]

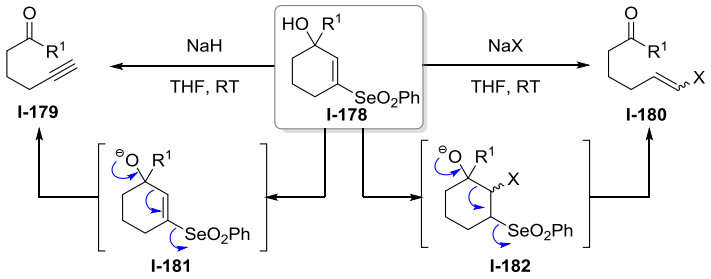


Scheme 35: Ring expansion of ethyl cyclohexanone-2-carboxylate with phenyl vinyl selenone.

[53] Ring opening : T. Sugawara, I. Kuwajima, *Tetrahedron Lett.* **1985**, *26*, 5571.

Fragmentation

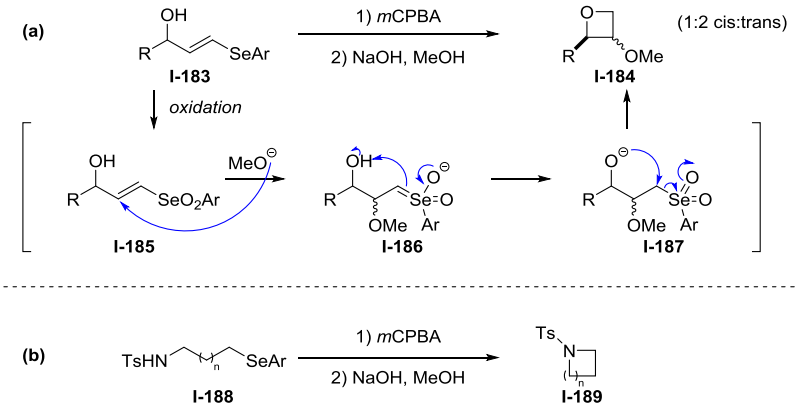
The peculiar reactivity of alkenyl selenone derivative has allowed also the fragmentation of some compounds. 3-(phenylselenonyl)cyclohex-2-en-1-ol **I-178** could afford two distinct linear products after fragmentation in function of the reaction condition applied. When NaH was used, the deprotonation of the alcohol promoted the ring opening of the 6-membered ring to deliver the alkyne **I-179**. On another hand, if a nucleophile was used, the Michael addition occurred and the resulting alkoxylate **I-182** would give the linear alkene **I-180** after fragmentation with release of benzeneseleninic acid. [54]



Scheme 36: Fragmentation of 1-substituted 3-(phenylselenonyl)cyclohex-2-en-1-ol.

Domino process

Other domino processes have been developed using the property of the organoselenium chemistry. Cascade reaction could be initiated by the oxidation of the selenide to afford the selenone derivative which could undergo a nucleophilic substitution when an internal nucleophile was present in the molecule. With this kind of domino reaction, oxetane **I-184** or cyclic amine **I-189** could be obtained (Scheme 37 (a) & (b)).[55]

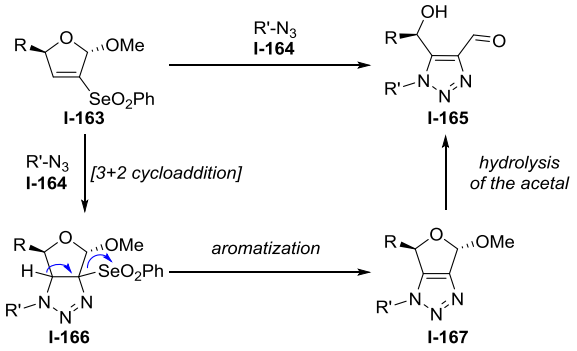


Scheme 37: Domino promoted by oxidation for the synthesis of cyclic amines and cyclic ethers.

[54] Fragmentation : M. Shimizu, R. Ando, I. Kuwajima, *J. Org. Chem.* **1981**, *46*, 5246; M. Shimizu, R. Ando, I. Kuwajima, *J. Org. Chem.* **1984**, *49*, 1230.

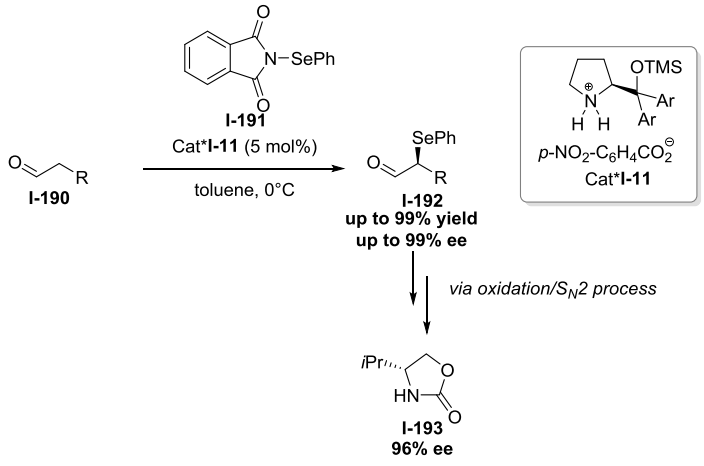
[55] Domino promoted by oxidation (a) M. Shimizu, I. Kuwajima, *J. Org. Chem.* **1980**, *45*, 4063 (b) A. Toshimitsu, H. Fuji, *Chem. Lett.* **1992**, *21*, 2017; M. Tiecco, L. Testaferri, A. Temperini, R. Terlizzi, L. Bagnoli, F. Marini, C. Santi, *Org. Biomol. Chem.* **2007**, *5*, 3510.

The synthesis of triazole has been described by Pathak in 2014. The [3+2] cycloaddition of the cyclic phenyl selenone **I-162** and alkyl azide **I-164** afforded the byclic compound **I-166**. After rearomatization with release of phenyl seleninic acid and hydrolysis of the cyclic acetal, densely functionalized triazoles **I-165** could be formed in moderate yield (Scheme 38).[56]



Scheme 38: [3+2] Cycloaddition/hydrolysis sequence of selenosugar.

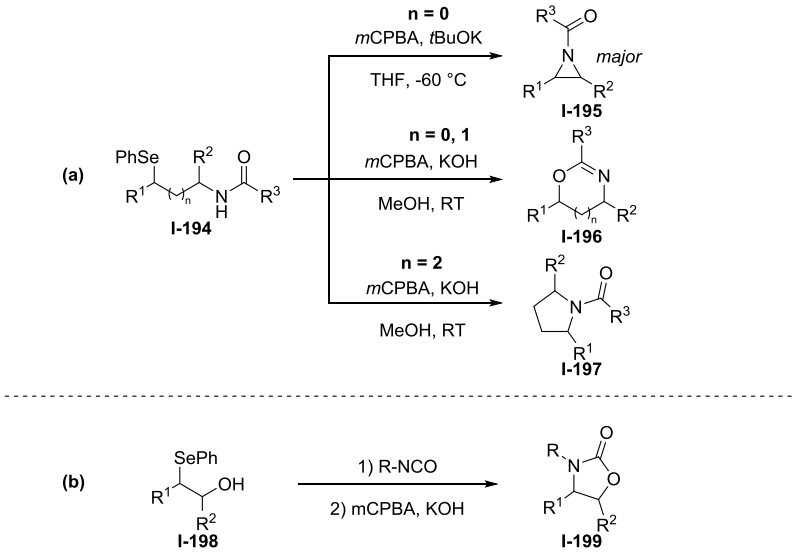
In view of elaborating enantioenriched domino sequences promoted by oxidation of selenide compound, it is important to stress that an enantioselective selenide incorporation was possible. Effectively, Melchiorre and Marini described the enantioselective organocatalytic α-selenation of aldehyde using *N*-(phenylseleno)phthalimide **I-191** and a chiral amine Cat***I-11** as catalyst. This reaction gave α-seleno aldehyde **I-192** in good yield and enantioselectivity and several optically active compounds could be synthesize using the versatile reactivity of selenium such as the oxidative domino process (Scheme 39 **(c)**).[57]



Scheme 39: Enantioselective α-selenation of aldehyde.

[56] A. Bhaumik, S. Samanta, T. Pathak *J. Org. Chem.* **2014**, *79*, 6895.
[57] M. Tiecco, A. Carlone, S. Sternativo, F. Marini, G. Bartoli, P. Melchiorre, *Angew. Chem. Int.Ed.* **2007**, *46*, 6882.

Some various heterocyclic compounds have also been synthesized using the oxidative domino process. Protected aziridine **I-195**, oxazolone **I-196**, protected pyrrolidine **I-197** or cyclic carbamate **I-199** could be isolated by this method (Scheme 40).[58]



Scheme 40: Domino promoted by oxidation for the synthesis of heterocycles.

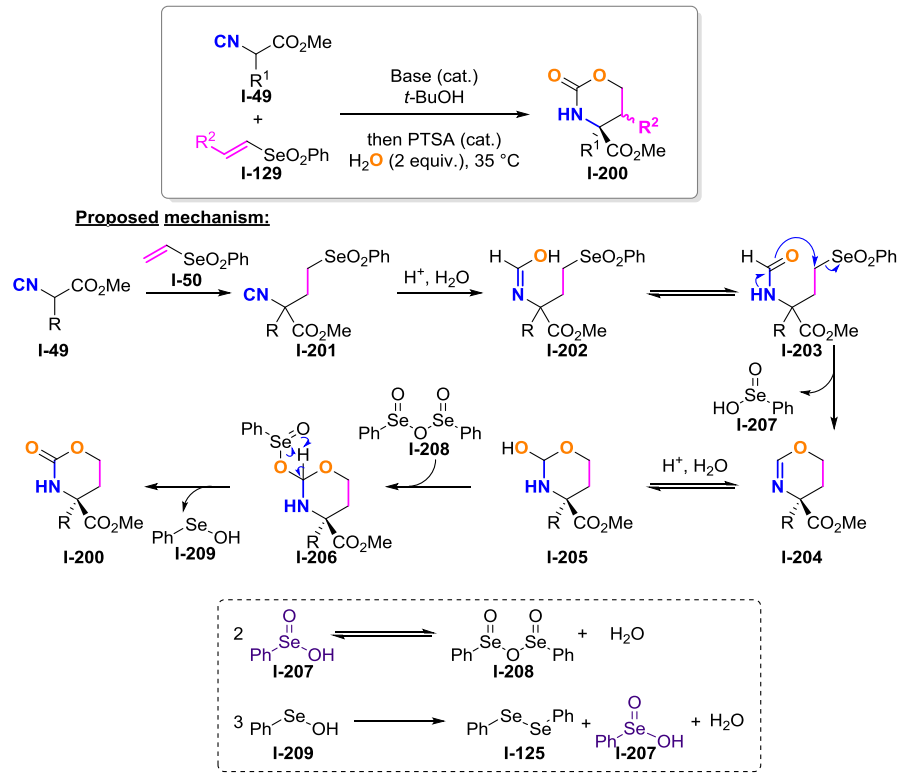
Multicomponent reaction

Multicomponent reactions using alkenyl selenone derivative have been likewise depicted. It was in 2014 that our group reported the multicomponent reaction of α-substituted α-isocyanoacetate **I-49**, phenyl vinyl selenone **I-50** and water in the presence of a Brønsted base followed by the addition of PTSA. In this transformation the phenyl selenonyl group has played three specific roles which were 1) an activator for the Michael addition, 2) a leaving group 3) the less common role, an oxidant.

The reaction pathway proposed for the one pot synthesis of 1,3-oxazinan-2-one began with the Michael addition and gave the adduct **I-201**, followed by the hydrolysis of the isonitrile which offered the formamide **I-203**. The formamide **I-203** displaced the phenyl selenonyl group which delivered the 5,6-dihydro-4H-1,3-oxazine **I-204** and benzenseleninic acid **I-207**. The benzeneseleninic acid **I-203** could dimerize to benzeneseleninic anhydride (BSA) **I-208**. A second addition of water gave 1,3-oxazinan-2-ol **I-205** which reacted with the benzeneseleninic anhydride to afford the seleninate **I-206**. After oxidation with elimination of benzeneselenenic acid **I-209** the desired oxazinan-2-one **I-200** was obtained (Scheme 41). [59] Three molecules of benzeneselenenic acid permited the formation of two molecules of

[58] (a) A. Toshimitsu, C. Hirosawa, S. Tanimoto, S. Uemura, *Tetrahedron Lett.* **1992**, *33*, 4017; V. R. Ward, M. A. Cooper, A. D. Ward, *J. Chem. Soc., Perkin Trans. 1* **2001**, *0*, 944 (b) M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini, C. Santi, *Chem. Eur. J.* **2004**, *10*, 1752;
[59] Multicomponent: (a) T. Buyck, Q. Wang and J. Zhu, *J. Am. Chem. Soc.* **2014**, *136*, 11524.

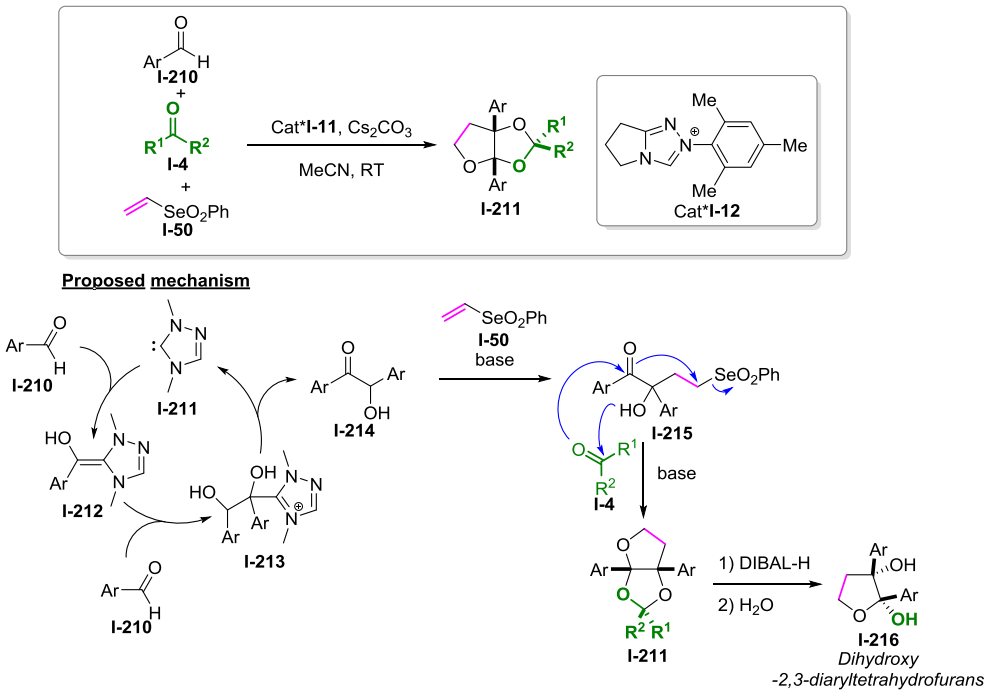
diphenyl diselenide, benzeneseleninic acid and water. This oxidation process with BSA has been reported in the 80s independently by Barton and Kuwajima. [60] It was notable that this example was the first time to describe phenyl vinyl selenone **I-50** with this triple role in the same reaction. With these abilities, complexity could be installed quickly on different scaffolds.



Scheme 41: Multicomponent reaction for the synthesis of cyclic carbamate.

Recently, Tiwari reported the multicomponent component reaction of aldehydes **I-210**, ketone **I-4** and phenyl vinyl selenone **I-50** in the presence of a base and NHC Cat***I-12** as catalyst. In the suggested mechanism, the NHC Cat***I-12** was catalyzing the reaction of two aldehydes **I-210** to produce the benzoin compound **I-214**. In the presence of a base this compound reacted with vinyl selenone to give the Michael adduct **I-215**. The alcohol group of this intermediate could attack the ketone **I-4** which after a cascade reaction afforded the bicyclic compound **I-211** (Scheme 42). An eventual deprotection of the acetal was possible by treating the cyclic acetal with DIBAL-H followed by a aqueous workup to isolate dihydroxy 2,3-tetrahydrofurane derivative **I-216**.[61]

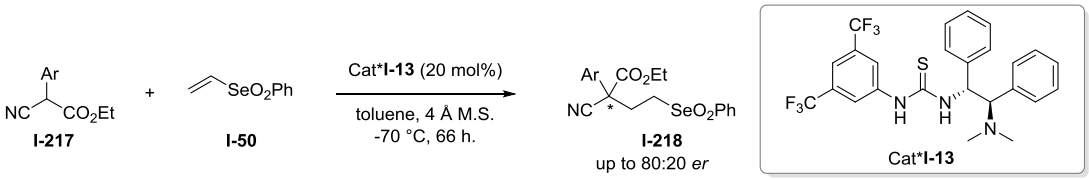
[60] Oxidation BSA: D. H. R. Barton, A. G. Brewster, R. A. H. F. Hui, D. J. Lester, S. V. Ley, T. G. Back, *J. Chem. Soc., Chem. Commun.* **1978**, *952*; M. Shimizu, I. Kuwajima, *Tetrahedron Lett.* **1979**, *20*, 2801; D. H. R. Barton, X. Lusinchi, P. Milliet, *Tetrahedron* **1985**, *41*, 4727.
[61] A. Bhaumik, R. S. Verma, B. Tiwari, *Org. Lett.* **2017**, *19*, 444.



Scheme 42: Multicomponent reaction using NHC and phenyl vinyl selenone.

Enantioselective transformation

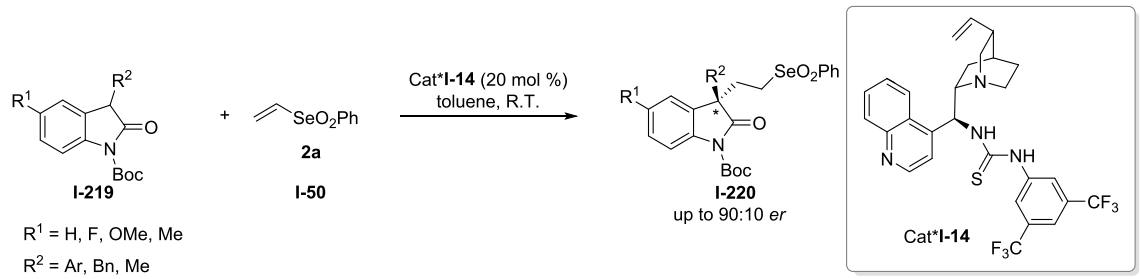
Enantioselective transformation using phenyl vinyl selenone **I-50** has been established and Marini and coworkers were the first to describe this Michael acceptor in an asymmetric conjugate addition (Scheme 43).[62] The 1,4-addition of α-aryl cyanoacetate **I-217** to phenyl vinyl selenone **I-50** in the presence of the bifunctional organocatalyst Cat***I-13** lead to α-aryl α-substituted cyanoacetate **I-218** with good yield and enantioselectivity.



Scheme 43: Asymmetric Michael addition of α-aryl α-substituted cyanoacetate to vinyl selenone.

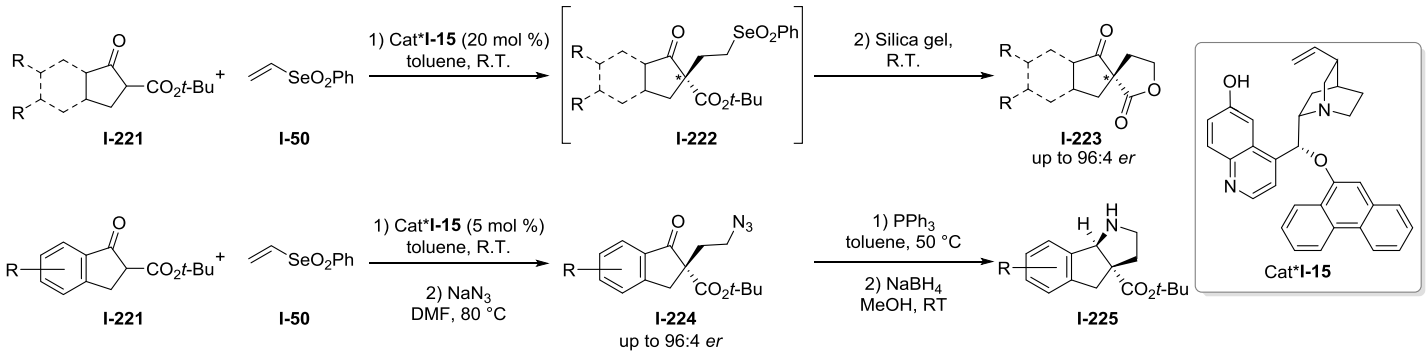
Chen and coworkers have shown in 2011 the asymmetric Michael addition of 3-substituted oxindole **I-219** to phenyl vinyl selenone **I-50** (Scheme 44). [63] In the presence of *Cinchona alkaloid* thiourea organocatalyst Cat***I-14**, the reaction afforded **I-220** in good yield and enantioselectivity.

[62] F. Marini, S. Sterativo, F. Del Verme, L. Testaferri, M. Tiecco, *Adv. Synth. Catal.* **2009**, *351*, 103.
[63] T. Zhang, L. Cheng, S. Hameed, L. Liu, D. Wang, Y.-J. Chen, *Chem. Commun.* **2011**, *47*, 6644.



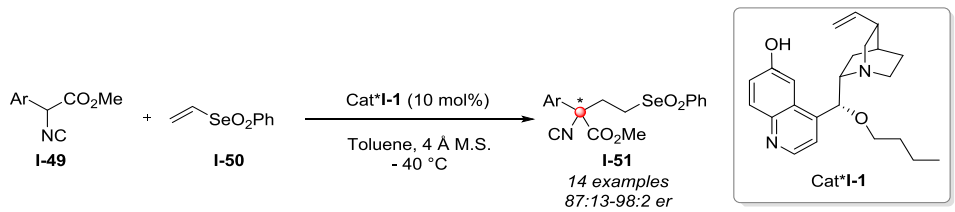
Scheme 44: Asymmetric Michael addition of 3-substituted oxindole to vinyl selenone.

The same year, Marini's group developed an enantioselective synthesis of spirolactones **I-223** by an organocatalyzed Michael-addition/cyclization sequence.[64] This reaction occured firstly with the conjugated addition of cyclic *tert*-butyl β-ketoester **I-221** to phenyl vinyl selenone **I-50**. Then, by taking advantages of the leaving group properties of the phenylselenonyl group, the desired spirolactones **I-223** were formed (Scheme 45 **(a)**). The synthesis of polycyclic pyrrolidines **I-225** was also possible by using an intramolecular Staudinger reaction/reduction sequence on the azide compound **I-224** (Scheme 45 **(b)**).



Scheme 45: Asymmetric Michael addition of cyclic *tert*-butyl β-ketoester to vinyl selenone.

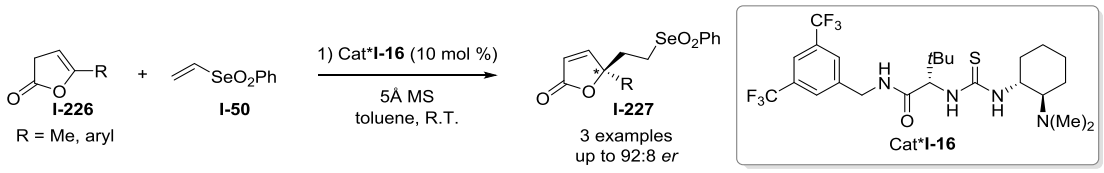
In 2013 our group described the catalytic asymmetric conjugate addition of α-aryl-α-isocyano acetate **I-49** to vinyl selenone **I-50** for the synthesis of quaternary α-amino acid derivatives.[14]



Scheme 46: Asymmetric Michael addition of α-aryl α-isocyanoacetate and phenyl vinyl selenone.

[64] S. Sternativo, A. Calandriello, F. Costantino, L. Testaferri, M. Tiecco, F. Marini, *Angew. Chem. Int. Ed.* **2011**, *50*, 9382; S. Sternativo, O. Walczak, B. Battistelli, L. Testaferri F. Marini *Tetrahedron* **2012**, *68*, 10536.

The last report has been depicted by Mukherjee last year where butenolides was used **I-226** as Michael donor in the enantioselective organocatalyzed conjugate addition with phenyl vinyl selenone **I-50** and thiourea-amine bifunctional organocatalyst Cat***I-16**.[65]



Scheme 47: Asymmetric Michael addition of butenolides and phenyl vinyl selenone.

Cinchona alkaloids as bifunctional organocatalyst.

Among the catalytic asymmetric approaches for the synthesis of enantioenriched compound, the organocatalysis has shown to be extremely attractive since the beginning of this century.[66] Environmentally friendly (low toxicity of the organocatalyst, development of metal free reaction), this type of catalyst has shown to be robust and not expensive which made them extremely popular to elaborate mild methodologies for the synthesis of potent bioactive molecules.

The family of *Cinchona* alkaloids, have been particularly employed in the organocatalyst field. Quickly introduced by Bredig and Fiske in 1912 for the hydrocyanation of aldehydes, this family of molecules were actually recognized as precious organocatalyst in the end of the seventies when Pracejus followed by Wynberg described the first enantioselective transformation using *cinchona* alkaloids in ketene chemistry or conjugated addition.[67]

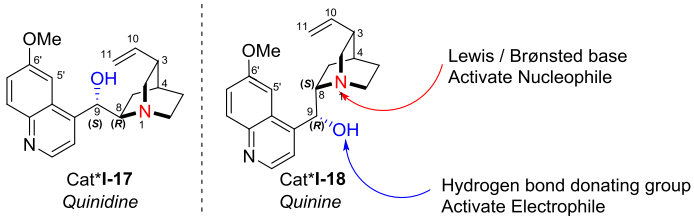
Quinidine Cat*I-**17** and quinine Cat***I-18**, two natural products from this alkaloid family, possessed the opposite stereocenters at the C_8 and C_9 position respectively (Scheme 48).[68] With this particularity, quinine and quinidine are considered as pseudoenantiomer.

[65] A. K. Simlandy, S. Mukherjee, *Org. Biomol. Chem.* **2016**, *14*, 5659.

[66] P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719; H. Pellissier, *Tetrahedron* **2007**, *63*, 9267; A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; U. Scheffler, R. Mahrwald, *Chem. Eur. J.* **2013**, *19*, 14346.

[67] G. Bredig, P. S. Fiske, *Biochem. Z.* **1912**, *46*, 7; H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9; H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, *16*, 4057; R. Helder, R. Arends, W. Bolt, H. Hiemstra, H. Wynberg, *Tetrahedron Lett.* **1977**, 18, 2181; S. Colonna, H. Hiemstra, H. Wynberg, *J. Chem. Soc., Chem. Commun.* **1978**, 238; H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417.

[68] (a) K. Kacprzak, J. Gawroński, *Synthesis* **2001**, *7*, 961; H. Martin, R. Hoffmann, J. Frackenpohl, *Eur. J. Org. Chem.* **2004**, *2004*, 4293; T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 7496; S. J. Connon, *Chem. Commun.* **2008**, *0*, 2499; T. Marcelli, H. Hiemstra, *Synthesis* **2010**, *8*, 1229.



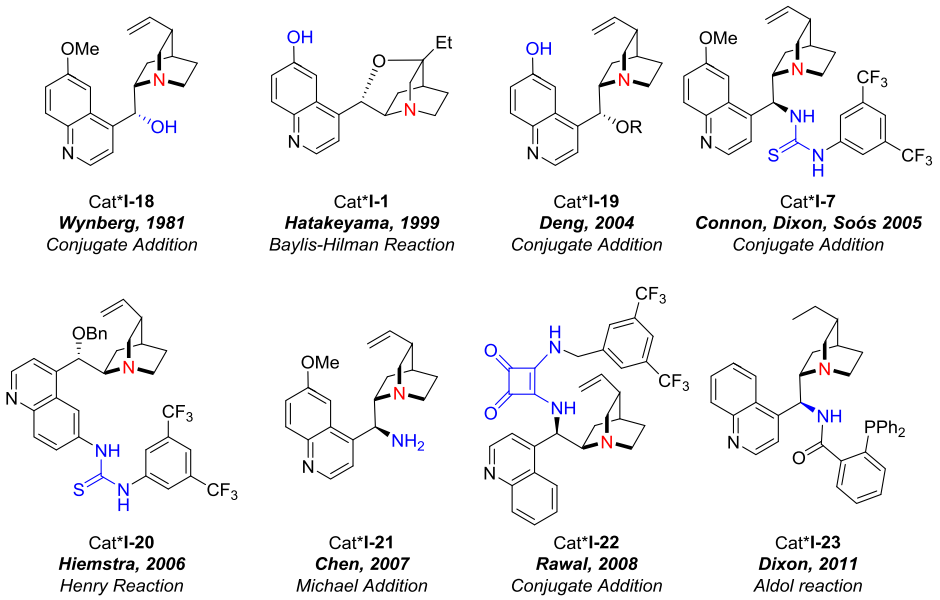
Scheme 48: Cinchona alkaloids, a bifunctional organocatalyst.

Cinchona alkaloids have been considered as bifunctional organocatalysts. They possess a basic nitrogen on the quinuclidine part which played the role of Lewis or Brønsted base to activate nucleophile and an hydroxyl group on the carbon C_9 which allows the activation of electrophile by hydrogen bonding (Scheme 48).[69]

The easy modification of this organic molecule (especially on the $C_{6'}$ and the C_9 position) and the presence of 5 stereogenic centers (N_1, C_4, C_3, C_8, C_9) on the *cinchona alkaloids* give to this compound a tuneable chiral environment. Different H-bond donor such as alcohol, amine, amide, thioruea, or squaramide have been installed at the $C_{6'}$ or C_9 position of the organocatalyst. With them, high degree of chiral induction has been reached and various methodologies have been developed to achieve the synthesis of important optically active molecules (Scheme 49).[70]

[69] A. G. Doyle, E. N. Jacobsen *Chem. Rev.* **2007**, *107*, 5713; M. S. Taylor, E. N. Jacobsen *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen *Chem. Eur. J.* **2011**, *17*, 6890; P. Chauhan, S. S. Chimni, *RSC Adv.* **2012**, *2*, 737.

[70] (a) H. Hiemstra, H. Wynberg *J. Am. Chem. Soc.* **1981**, *103*, 417; (b) Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama *J. Am. Chem. Soc.* **1999**, *121*, 10219; (c) H. Li, Y. Wang, L. Tang, L. Deng *J. Am. Chem. Soc.* **2004**, *126*, 9906; (d) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun* **2005**, 4481; S. H. McCooey, S. J. Connon *Angew. Chem. Int. Ed.* **2005**, *44*, 6367; B. Vakulya, S. Varga, A. Csámpai, T. Soós *Org. Lett.*, **2005**, *7*, 1967; (e) T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra *Angew. Chem. Int. Ed.* **2006**, *45*, 929; (f) J. -W. Xie, W. Chem, R. Li, M. Zeng, W. Du, L. Yue, Y. -C. Chen, Y. Wu, J. Zhu, J. -G. Deng *Angew. Chem. Int. Ed.* **2007**, *46*, 389 (g) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416; (h) F. Sladojevich, A. Trabocchi, A. Guarna, D. J. Dixon, *J. Am. Chem. Soc.* **2011**, *133*, 1710.

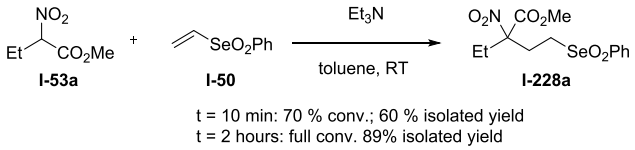


Scheme 49: Modification of *Cinchona alkaloid* over the years

Results & Discussion

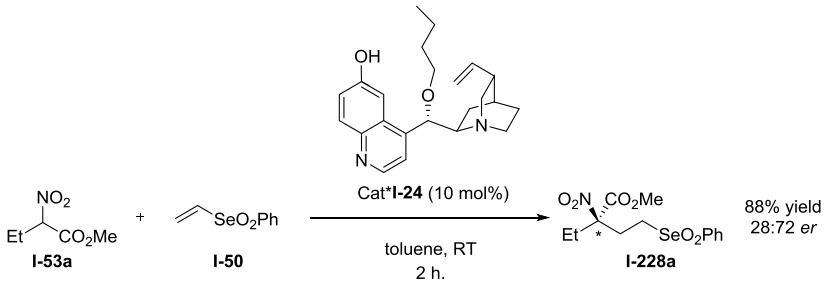
Reaction Optimization

In order to answer to the scope restriction observed in the methodology developed with α-aryl α-isocyanoacetate **I-49** and phenyl vinyl selenone **I-50**,[14] we started to study the racemic condition of the Michael addition with methyl nitrobutyrate **I-53a**, phenyl vinyl selenone **I-50** and triethylamine at room temperature in toluene (Scheme 50). After 10 min of reaction, 70% of the phenyl vinyl selenone was converted to the desired product **I-228a**, which was isolated in 60% yield. After 2 hours and full conversion of the reagents, the product was isolated in 89% yield.



Scheme 50: Racemic Michael addition of methyl nitrobutyrate to phenyl vinyl selenone.

To perform the reaction in a catalytic enantioselective way, the *Cinchona* alkaloid-based organocatalyst Cat***I-24** with a free OH in $C_{6'}$ position was used. This organocatalyst firstly introduced by Deng and co-worker[71] appeared also to be one of the best catalyst for our synthesis of α,α-disubstituted α-isocyanoacetate **I-51**.[14] Using 10 mol% of the organocatalyst in toluene at room temperature, the desired product **I-228a** was isolated with a yield of 88% and an enantiomeric ratio of 28:78 (Scheme 51).



Scheme 51: First hit for the asymmetric Michael addition of methyl nitrobutyrate to phenyl vinyl selenone.

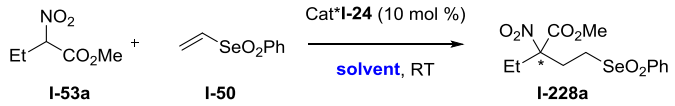
With this promising result in hand, the optimization of α,α-disubstituted α-nitroacetate **I-228** synthesis was investigated by varying the different parameters of the reaction.

[71] (a) F. Wu, H. Li, R. Hong, L. Deng, *Angew. Chem., Int. Ed.* **2006**, *45*, 947. (b) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948. (c) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem., Int. Ed.* **2005**, *44*, 105. (d) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906.

Solvents

Different solvents were screened. Polar solvent such as THF gave poor enantioselectivity. Apolar solvents gave better *er* and toluene appeared to be the best solvent (Table 1).

Table 1: Solvent screening.



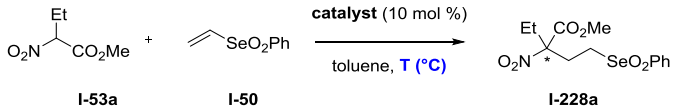
I-53a I-50 I-228a

Entry	Catalyst	Conditions	Isolated Yield (%)	*er*
1	Cat***I-24**	**Toluene**, 2 h.	88 %	28:72
2	Cat***I-24**	**THF**, 16 h.	81 %	44:56
3	Cat***I-24**	**DCM**, 16 h.	72 %	34:66
4	Cat***I-24**	**Xylene**, 2 h.	95 %	31:69

Temperature screening

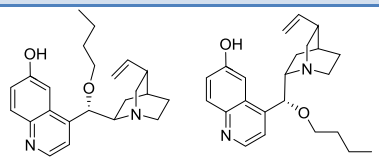
The temperature of the reaction was explored (Table 2). When the temperature was reduced, the enantioselectivity of the catalytic Michael addition increased, but the conversion of the reaction was slower. It was also important to note that the pseudoenantiomer quinine derivative Cat***I-1** gave better enantiomeric ratio in comparison with quinidine derivative Cat***I-24** with an inversion of the major enantiomer.

Table 2: Temperature screening.



I-53a I-50 I-228a

Entry	catalyst	Condition	Isolated Yield (%)	*er*
1	Cat***I-24**	**0 °C**, 4 h.	92	20:80
2	Cat***I-24**	**- 15 °C**, 16 h.	88	16:84
3	Cat***I-24**	**- 30 °C**, 48 h.	92	12:88
4	Cat***I-24**	**- 40 °C**, 24 h.	30	12:88
5	Cat***I-1**	R.T., 2 h.	94	85:15
6	Cat***I-1**	**- 30 °C**, 48 hours	96	92:8
7	Cat***I-1**	**- 40 °C**, 72 hours	82	93:7



Cat***I-24** Cat***I-1**

Finally, after 48 hours of reaction with the organocatalyst Cat***I-15** at - 30 °C, the α,α-disubstituted α-nitroacetate **I-228a** was synthesized with a yield of 96 % and an enantioselective ratio of 92:8 (Entry 6).

Catalyst screening

The synthesis of different organocatalysts has been depicted in the Scheme 52. Starting from Quinine Cat***I-18**, the OH on the C_9 position could be convert to NH_2 using a one pot Mitsunobu/Staudinger reaction. The subsequent C_9-aminoquinine Cat***I-21** could be converted to the thiourea *cinchona* alkaloid Cat***I-8** using 3,5-bis(trifluoromethyl)phenyl isothiocyanate.

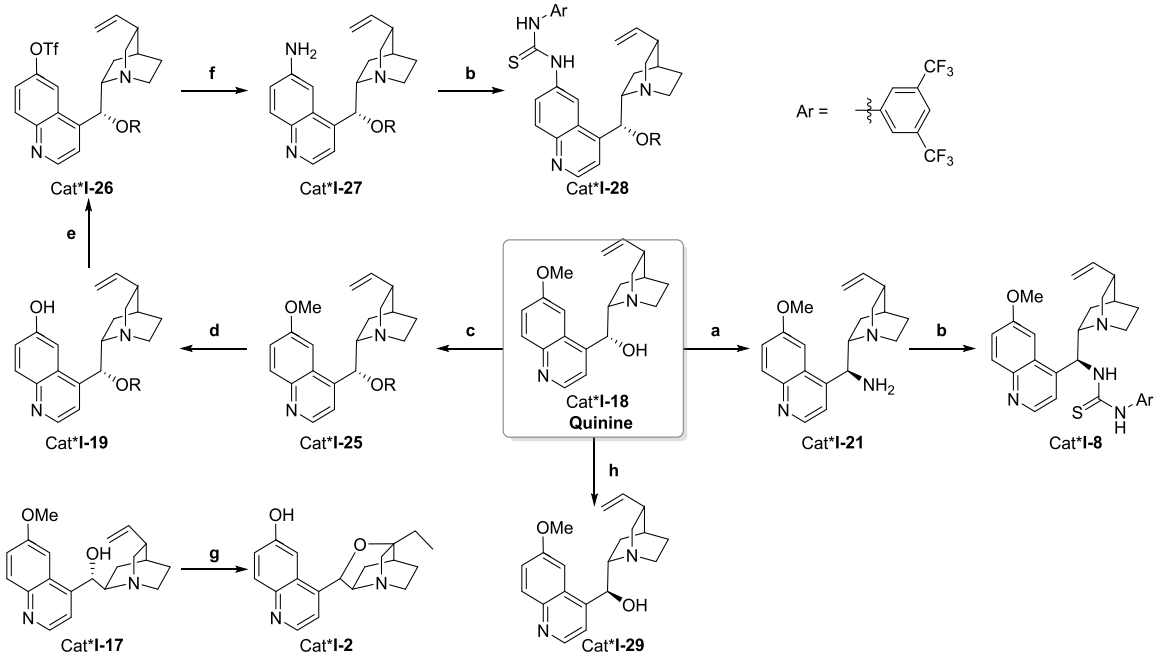
Quinine Cat***I-18** could also be converted to C_9-O-substituted derivatives. C_9-O-alkylated Cat***I-25** was made by S_N2 with alkyl halide. C_9-O-arylated Cat***I-25** was elaborated with Ullmann coupling.

The $C_{6'}$ position could also be modified after deprotection of the alcohol (Scheme 52,step d). Triflation of the C6' alcohol of Cat***I-19** allowed the insertion of amine or thiourea at this position and offered quinine derivative Cat***I-27** and Cat***I-28** respectively.

β-isocupreine Cat***I-2**, a twistane-like structure, has shown to be a good organocatalyst candidate in some transformation due to its constrained tricyclic cage. β-ICPD Cat***I-2** could be synthesized from quinidine using KBr in concentred H_3PO_4.

Finally the C_9-epi-quinine Cat***I-29** could be obtained using a Mitsunobu reaction with *para*-(nitro)benzoic acid. After the hydrolysis of the subsequent ester, the epi-quinine Cat***I-29** could be isolated with an invertion of the stereocenter C_9.[70,72]

[72] For the synthesis of C_9 epi-quinine S. Debarge, S. Thibaudeau, B. Violeau, A. Matin-Mingot, M.-P. Jouannetaud, J.-C. Jacquesy, A. Cousson, *Tetrahedron* **2005**, *61*, 2065.

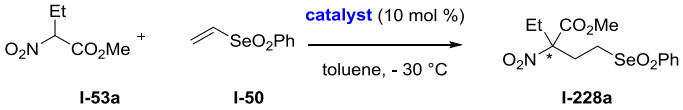


a) DIAD, PPh_3, DPPA, THF/H_2O (3:1) **b)** ArNCS, THF, RT **c**) *for aryl*, ArI, CuI (10 mol%), phenantroline /20 mol%), Cs_2CO_3, toluene, 130 °C , *for alkyl*, RX, NaH DMF, 40 °C **d)** NaH, EtSH DMF, 110 °C **e)** $PhNTf_2$, DMAP, DCM **f)** $Pd(OAc)_2$, BINAP, Cs_2CO_3, benzophenone imine, THF, reflux **h)** p-NO_2-benzoic acid, DEAD, PPh_3, THF, K_2CO_3, MeOH reflux **g)** KBr, H_3PO_4, RT

Scheme 52: Synthesis of *Cinchona alkaloids* derivatives

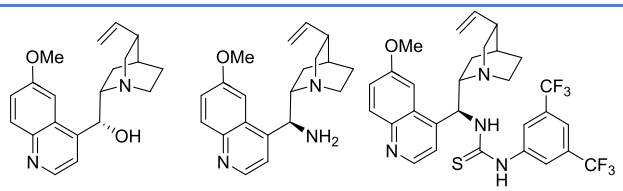
A first serie of Cinchona alkaloid were investigated (Table 3). Whereas quinine Cat***I-18** and thiourea derivative Cat***I-8** gave low enantioselectivity (entries 1 and 3); cupreine Cat***I-30**, β-isocupreidine Cat***I-2**, amino derivative Cat***I-21** and Cat***I-15** lead to good enantiomer ratio (entries 1, 2, 4 and 6). However, the yield obtained with cupreine Cat***I-30** and Cat***I-21** are low (65 and 25% respectively) (entries 2 and 3).

Table 3: Catalyst screening.

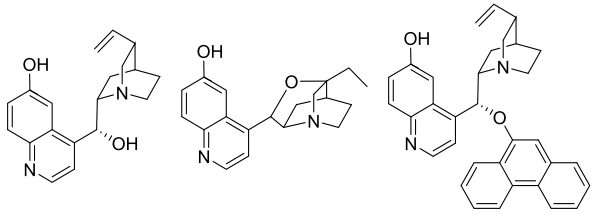


I-53a I-50 I-228a

Entry	Catalyst	Time	Isolated Yield (%)	*er*
1	Cat***I-18**	72 h.	84	56:46
2	Cat***I-30**	48 h.	65	87:13
3	Cat***I-21**	72 h.	25	90:10
4	Cat***I-2**	48 h.	96	20:80
5	Cat***I-8**	48 h.	15	34:66
6	Cat***I-15**	48 h.	84	94:6



Cat***I-18** Cat***I-21** Cat***I-8**



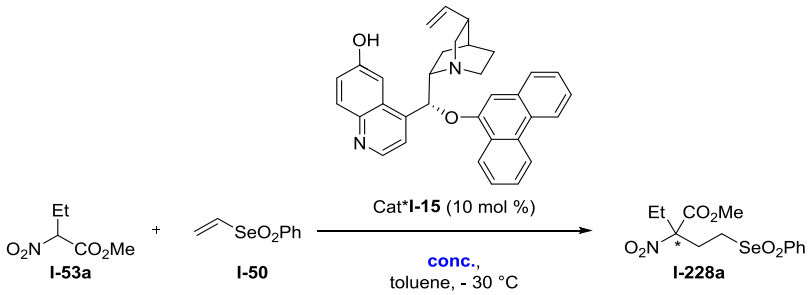
Cat***I-30** Cat***I-2** Cat***I-15**

This first organocatalyst screening gave Cat***I-2** as the best catalyst which produced **I-228a** in 84% with 94:6 *er* (Entry 6).

Concentration screening

The concentration of the reaction was then investigated (Table 4). Even if the concentration was increased, no big changes were observed for the yield and the enantioselectivity of the reaction. We have fixed the concentration to 0.1 M for the subsequent study.

Table 4: Concentration screening.

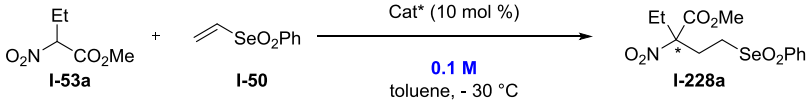


Entry	Catalyst	Concentration	Isolated Yield (%)	*er*
1	Cat***I-15**	**0.1 M**	84	6:94
2	Cat***I-15**	**0.25 M**	86	6:94
3	Cat***I-15**	**0.5 M**	72	7:93

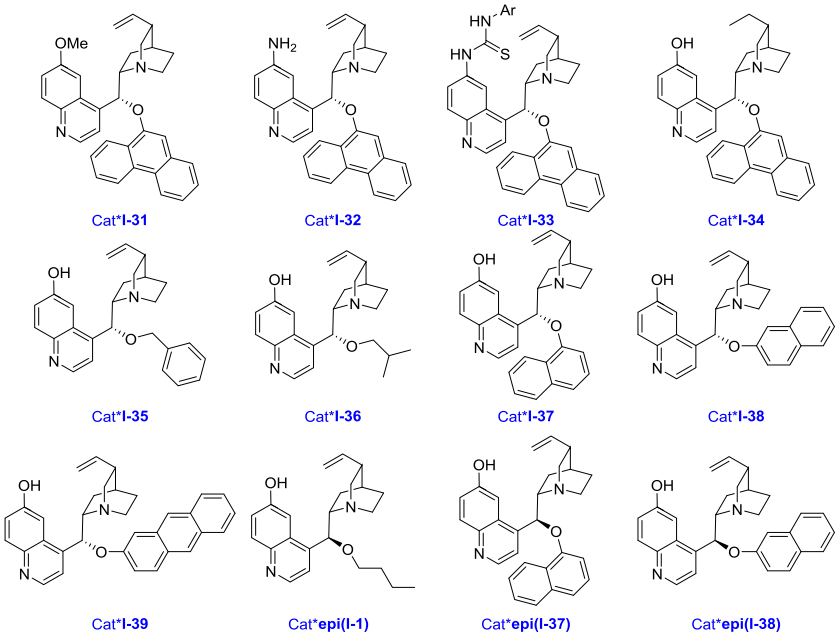
Fine tuning catalyst

Other organocatalysts were used (Table 5). After varying the group at $C_{6'}$-position with OMe, OH, NH_2 or thiourea (Entry 1 to 4), the phenol group at this position (Entry 1) appeared to be an efficient catalyst for our enantioselective Michael addition. The *Cinchona* alkaloid derivative Cat***I-34**, where the vinyl double bond of the catalyst was reduced, did not impact the enantioselectivity and gave similar yield and *er* as the catalyst Cat***I-15** (Entry 5).

Table 5: Other catalysts screening.



Entry	Catalyst	Isolated Yield (%)	*er*
1*	Cat***I-15**	88	94:6
2	Cat***I-31**	60	51:49
3	Cat***I-32**	10	57:43
4	Cat***I-33**	27	74:26
5	Cat***I-34**	80	90:10
6	Cat***I-35**	58	82:18
7	Cat***I-36**	99	94:6
8	Cat***I-37**	87	95.5:4.5
9	Cat***I-38**	96	96:4
10	Cat***I-39**	97	95:5
11	Cat***epi(I-1)**	99	95:5
12	Cat***epi(I-37)**	90	95:5
13	Cat***epi(I-38)**	74	94:6



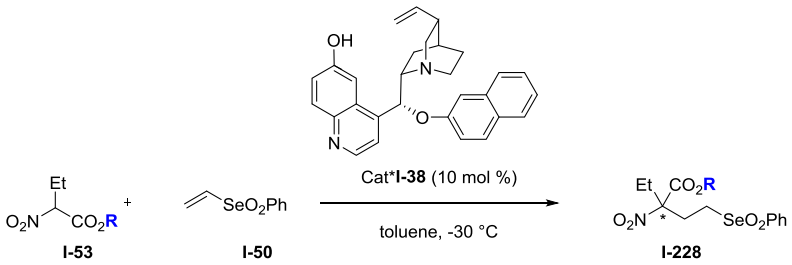
The 9-phenanthryl moiety at the C_9 position of the organocatalyst was then replaced by different bulky aryl and alkyl groups (Entries 6 to 10). Except catalyst Cat***I-35** which possessed an OBn on C_9, all the orgacatalysts gave high enantioselectivity. Intriguingly, the absolute configuration at C_9 seemed not to be important for the catalytic activities of the

catalysts since the Cat***epi(I-15)**, Cat***epi(I-37)** and Cat***epi(I-38)** were all efficient catalysts affording the adduct in good to excellent yields with *er* higher than 94:6 (entries 13–15). Overall, the best conditions consisted to perform the reaction of **I-53a** and **I-50** in toluene at -30 °C for 48 h in the presence of catalyst Cat***I-38**. Under these conditions, the Michael adduct **I-228a** was isolated in 96% yield with an *er* of 96:4.

Ester screening

The effect of the alkyl residue of ester was evaluated under the optimum conditions (Table 6). While comparable enantioselectivities were observed with the methyl and ethyl esters (Entry 1 & 2), the reaction of the *tert*-butyl ester **I-53c** with **I-50** afforded the Michael adduct **I-228c** with significantly reduced *er* (Entry 3).

Table 6: Effect of the ester size on the enantioselectivity of the reaction.



Entry	CO_2R	Isolated Yield (conv.)	*er*
1	CO_2**Me (I-228a)**	96%	96:4
2	CO_2**Et (I-228b)**	93%	95:5
3	CO_2***t*-Bu (I-228c)**	76%	54:46

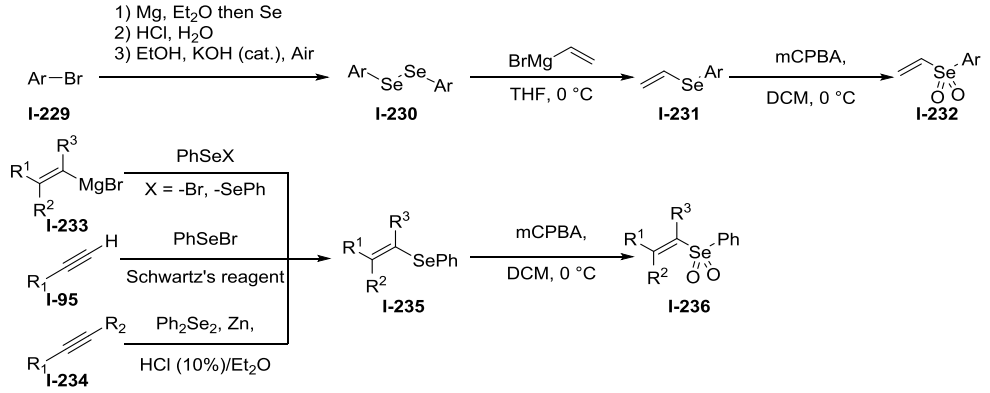
It is notable that some additives (Na_2SO_4, molecular sieves…) were added in the reaction but no influence on the yield or enantioselectivity was noticed. Finally, the best conditions for this catalytic enantioselective Michael Addition on phenyl vinyl selenone were with methyl α-substituted nitroacetate at – 30 °C in toluene in the presence of 10 mol% of bifunctional organocatalyst Cat***I-38**.

Scope

To determine the possible variation allowed on the Michael acceptor, different alkenyl aryl selenone derivative were synthesized. The introduction of other aryl group on the selenone was made from arylbromide **I-229** which was firstly converted to a Grignard reagent. After selenation with pure selenium the reaction was quenched with HCl to afford the aryl selenol which dimerized few hours later to the diaryl diselenide **I-230**. The diaryl

diselenide **I-230** was converted to the aryl vinyl selenone **I-232** using the same procedure than with phenyl vinyl selenone **I-50**.[73]

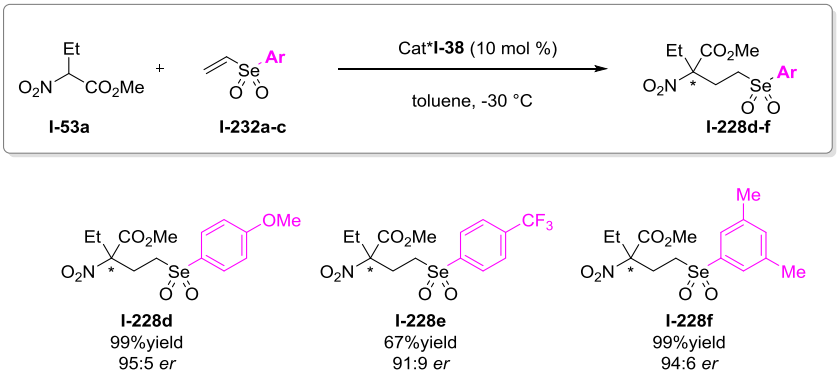
For the alkenyl part, different approaches have been reported. The most common method was with the Grignard reaction of an alkenyl magnesium bromide to phenylselenyl bromide or diphenyl diselenide and gave alkenyl phenyl selenide **I-235**. Another possibility was the hydrozirconation of terminal alkyne **I-95** with the Schwartz's reagent. The zirconium species was treated with phenylselenyl bromide to afford derivative **I-235**.[74] Finally, the synthesis of alkenyl phenyl selenide could also be performed using alkynes **I-234**, diphenyl diselenide, zinc and a biphasic acidic medium.[75] The alkenyl phenyl selenides **I-235** were converted to alkenyl phenyl selenone **I-236** using 2 equivalents of *m*-CPBA (Scheme 53).



Scheme 53: Synthesis of different alkenyl aryl selenones

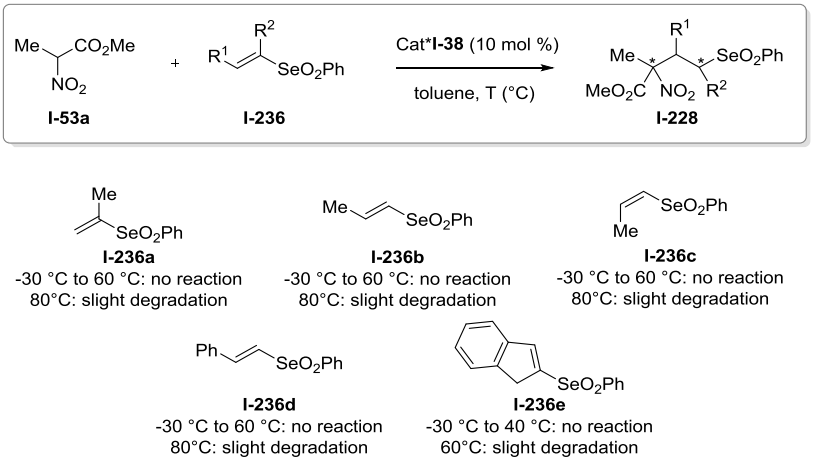
With the new Michael acceptors and our optimal conditions in hand, the scope of the reaction was next examined. For the aryl group attached to the selenium, The presence of electron-donating group such as *para*-methoxy or bulky aryl such as 3,5-dimethylphenyl did not influence the reaction and gave similar yield and enantioselectivity. However, electron-withdrawing group such as trifluoromethyl in *para* position gave slightly lower enantioselectivity and yield.

[73] K. B. Sharpless, M. W. Young, *J. Org. Chem.* **1975**, *40*, 947; H. J. Reich, W. W. Willis Jr., P. D. Clark, *J. Org. Chem.* **1981**, *46*, 2775; L. Bagnoli, C. Scarponi, L. Testaferri, M. Tiecco, *Tetrahedron: Asymmetry* **2009**, *20*, 1506.
[74] P. Burch, M. Binaghi, M. Scherer, C. Wentzel, D. Bossert, L. Eberhardt, M. Neuburger, P. Scheiffele, K. Gademann, *Chem. Eur. J.* **2013**, *19*, 2589.
[75] C. Tidei, L. Sancineto, L. Bagnoli, B. Battistelli, F. Marini, C. Santi, *Eur. J. Org. Chem.* **2014**, 5968.



Scheme 54: Scope of the aryl vinyl selenone.

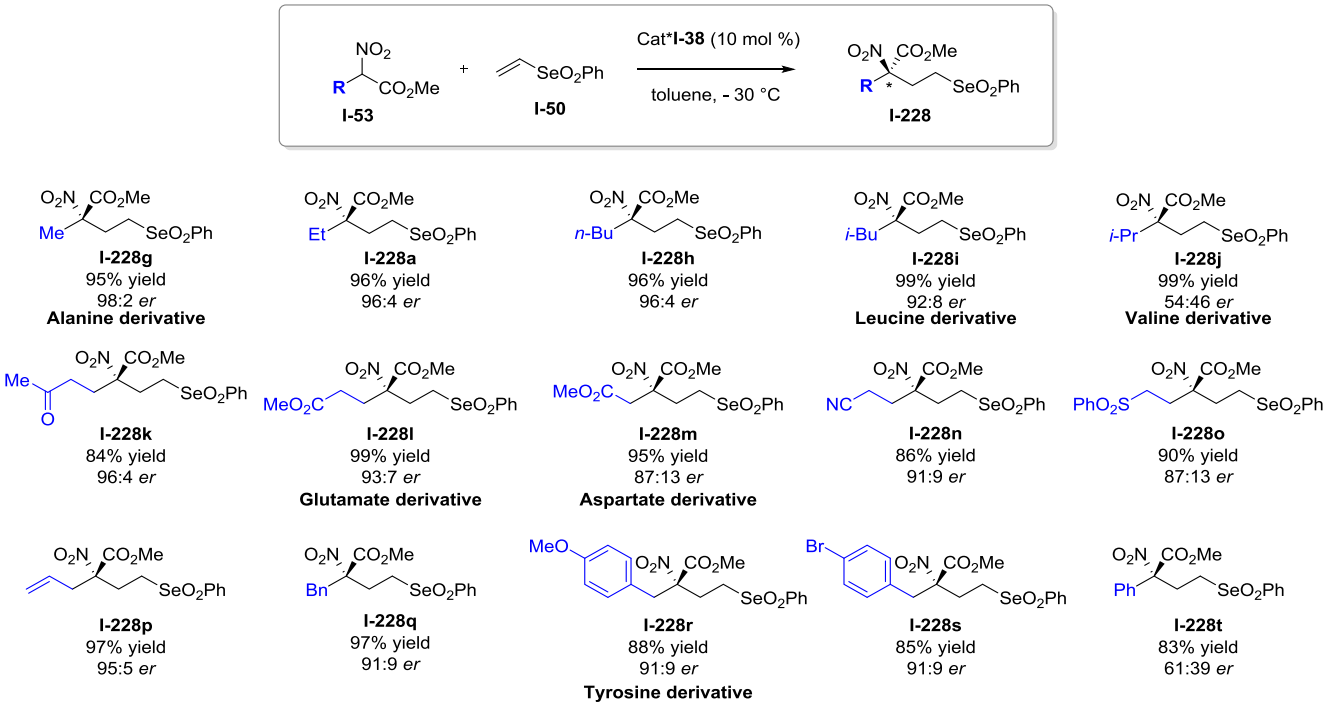
Different alkenyl phenyl selenone **I-236** were also tried as Michael acceptor for the asymmetric conjugate addition of α-substituted nitroacetate (Scheme 55). When the reaction was run with a α– or β– substituted alkenyl phenyl selenone (**I-236a**, **I-236b** and **I-236c**) and even if the reaction was heated to 60 °C no transformation was observed. If the reaction was heated to 80 °C the slight degradation of starting materials was detected (Entries 1-3). Other substrates such as (*E*)-(2-(phenylselenonyl)vinyl)benzene **I-236d** and 2-(phenylselenonyl)-1H-indene **I-236e** were also used as Michael acceptor partner. Similar results were obtained, no reaction occurred between – 30 °C and 60 °C (or 40 °C for **I-236e**). The same observation was also noted and when the reaction mixture was heated too much, the starting materials started to decompose.



Scheme 55: Other alkenyl phenyl selenone as Michael acceptor.

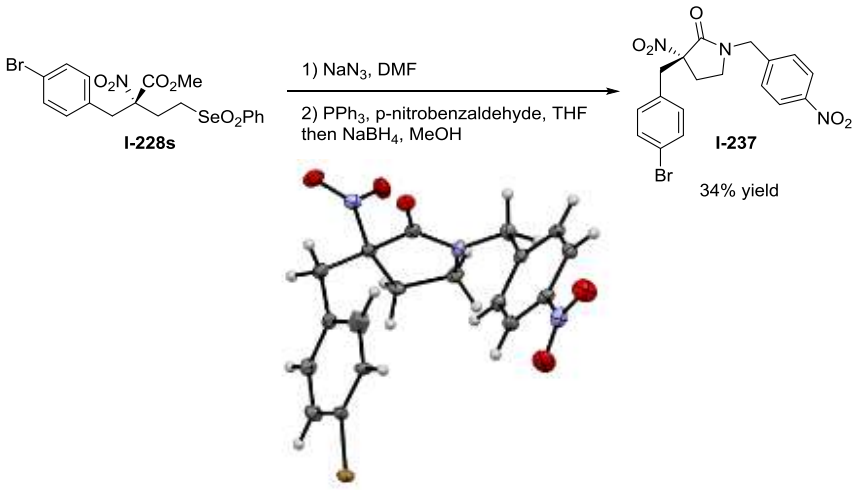
To continue our investigation on the scope of the catalytic enantioselective Michael addition, the variation of the α-substituted nitroacetate was studied. It appears that various types of alkyl, with or without functionalities were tolerated. Simple linear alkyl group (**I-228a, I-228g** and **I228h**) or branched alkyl group (**I-228i**) gave good enantioselectivity and yield. A variety of functionalities were compatible with our reaction conditions such as ketone

(**I-228k**), cyano (**I-228n**), phenylsulfonyl (**I-228o**), double bond (**I-228p**) and ester (**I-228l** and **I-228m**). Remarkably, some of our compounds (**I-228l**, **I-228m**, **I-228m**, **I-228o**) were clear precursors of α-substituted analogues such as aspartic acid, asparagine, glutamic acid, glutamine, arginine, methionine and proline. Benzyl substituent and its functionalized ones were compatible with the reaction to afford **I-228q-s**, surrogates for α-substituted phenylalanine and tyrosine. However, when methyl α-phenyl α-nitroacetate **I-53t** or methyl α-isopropyl α-nitroacetate **I-53j** was used in the enantioselective Michael addition almost no selectivity was observed. We supposed that the presence of a tertiary carbon in β of the α-nitroacetate **I-53** impeded a good chiral induction of the organocatalyst.



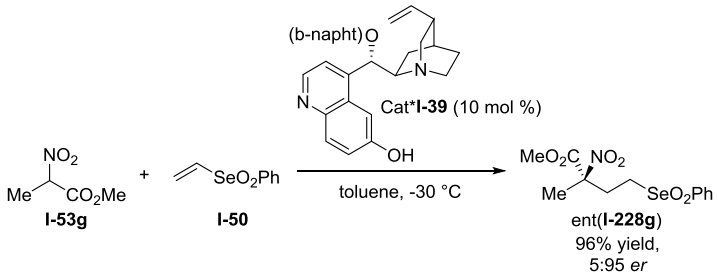
Scheme 56: Scope of the enantioselective Michael addition

To determine the stereochemistry of the major enantiomer, a crystalline compound was mandatory to perform an X-ray analysis. For that, treatment of **I-228s** with NaN_3 followed by aza-Wittig reaction of the resulting azido compound with 4-nitrobenzaldehyde and reductive cyclization afforded gratefully the crystalline pyrrolidinone **I-237**. The structure of **I-237** was solved by X-ray crystal structural analysis and the absolute configuration of the quaternary center was determined to be (S) unambiguously. Consequently, stereoselectivity of the precursor **I-228s** and the Michael adducts **I-228** obtained with the methodology were assigned accordingly.



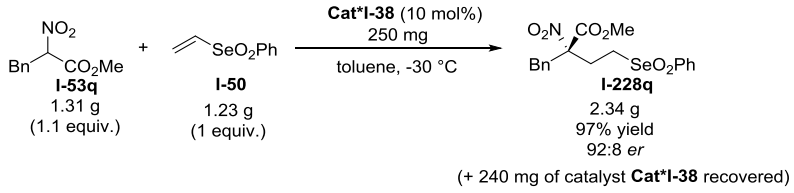
Scheme 57: Synthesis and X-ray structure of the pyrrolidinone I-237.

The quinidine derivative Cat***I-39**, pseudoenantiomer of the quinine derivative Cat***I-38**, was used as the organocatalyst under the same reaction conditions. As expected, the formation of the other enantiomer ent(**I-228g**) was favoured with similar yield and a slightly lower enantioselectivity (Scheme 58).



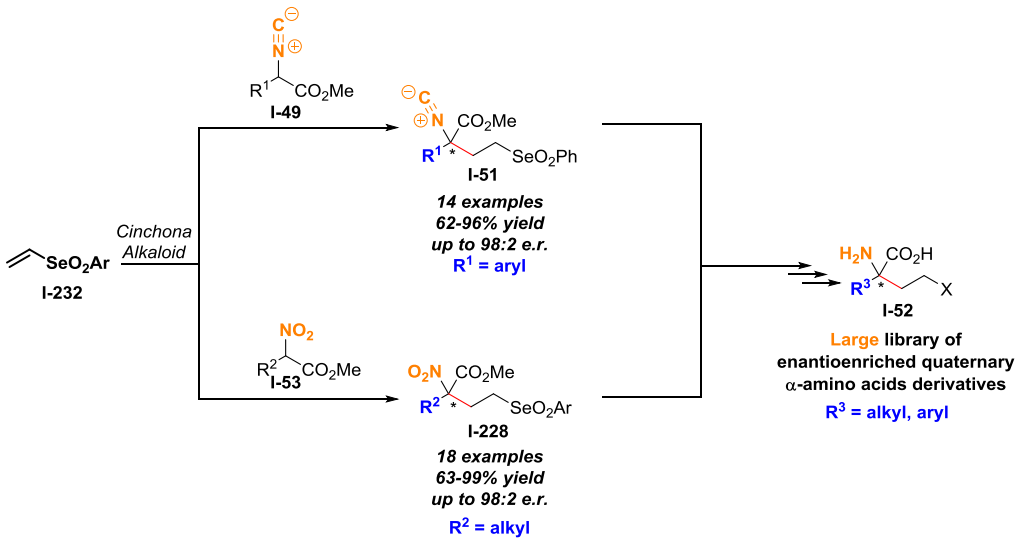
Scheme 58: Michael addition catalyzed by quinidine-derived catalyst.

Performing the reaction of **I-53q** with **I-50** in a gram scale afforded the Michael adduct **I-228q** in similar yield and enantioselectivity (Scheme 59). In this case, it was notable that almost all the catalyst Cat***I-38** was easily recovered (96 %) and could be re-used without diminishing the catalytic efficiency.



Scheme 59: Gram scale enantioselective Michael addition.

The large scope of this asymmetric Michael addition of α-substituted α-nitroacetate **I-53** to phenyl vinyl selenone **I-50** has shown the possibility of synthesizing various optically active precursors of tetrasubstituted α-amino acids. Even if α-aryl α-nitroacetates gave low enantioselectivity under our reaction condition, this methodology appeared to be a complementary tool to the method based on α-aryl α-isocyanoacetates **I-49** previously developed. [14] With both of these methodologies, the access to a broad range of quaternary α-amino **I-52** acids is possible (Scheme 60).



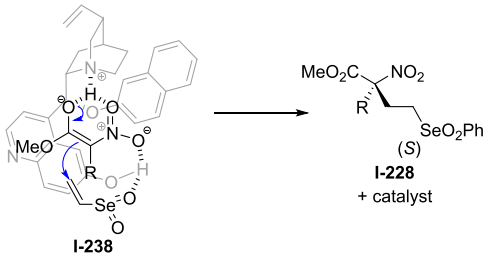
Scheme 60: Development of two complementary methodologies for the synthesis of enantioenriched quaternary α-amino acids

Transition state

In this transformation, organocatalysts with a free OH group at $C_{6'}$ have induced high enantioselectivity. This result implied that hydrogen bonding might take place with the substrate. Since nitro group was known to have a strong tendency to form hydrogen bonds with even a slightly acidic proton,[76] a stereochemical model (Figure 1) implicating an enolate of methyl α-substituted α-nitroacetate was proposed following the transition state and the computational studies reported on bifunctional organocatalysts[77] and $C_{6'}$OH-cinchona alkaloid derivative (Scheme 61). [14,71,78] In the proposed transition state **I-238**, we suggested that the protonated *cinchona alkaloids* would adopted, in nonpolar solvent, an anti-open conformer.[79] The positioning of the two reactants was also fixed by the hydrogen bond

[76] Hydrogen bond with nitro group: W. F. Baitinger, P. von R. Schleyer, T. S. S. S. R. Murty, L. Robinson, *Tetrahedron* **1964,** *20*, 1635
[77] Bifunctional mechanism: A. Hamza, G. Schubert, T. Soós, I. Papái, *J. Am. Chem. Soc.* **2006**, *128*, 13151 B. Kótai, A. Hamza, V. Farkas, I. Papái, T. Soós, Chem. Eur. J. **2014**, *20*, 5631; P. Hammar, T. Marcelli, H. Hiemstra, F. Himo *Adv. Synth. Catal.* **2007**, *349*, 2537.
[78] Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 3928.
[79] Anti open conformer of *Cinchona alkaloid*: G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, J. S. Svendsen, I. Marko, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 8069.

formed between the OH group at $C_{6'}$ and the nitro and the selenonyl group respectively. A pseudo-intramolecular *Si*-face attack of enolate to the vinyl selenone would deliver, after protonation, the Michael adduct **I-228** with an absolute configuration of *S*. In this proposal, the alkyl residue of the ester could have a steric interaction with the quinoline subunit of the catalyst. Therefore, increasing the size of the R group would destabilize this transition state, thus leading to a diminished enantioselectivity which was described on the Table 6. The O-naphyl group present on the C9 seemed also to shield the substrates and induce chiral interaction.

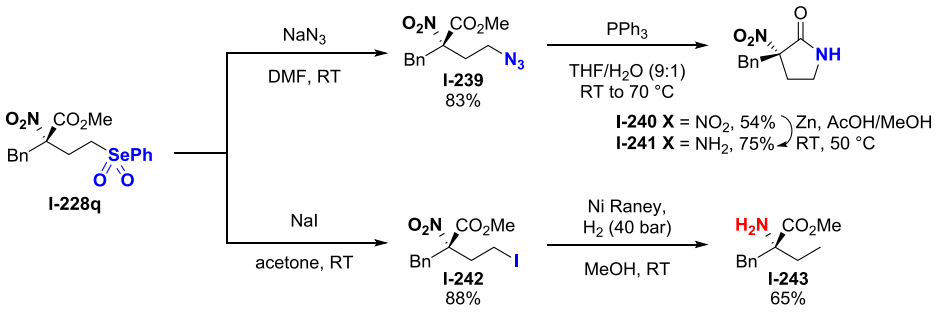


Scheme 61: A proposed transition-state model with the stereoselectivity observed

Post-transformation

To reach important enantioenriched building blocks, chemical transformations of α,α-disubstituted α-nitroacetate were envisaged by taking advantage of the reactivity of the nitro and phenylselenonyl groups (Scheme 107).[30,80,81] Reaction of **I-228q** with NaN_3 afforded the azido derivative **I-239** which, upon Staudinger reduction and lactamization cascade, furnished the pyrrolidinone **I-240**. The latter was further reduced to the amino derivative **I-241**, a constrained analogue of phenylalaninamide, the enantioselective synthesis of which remained unknown.[82] Substitution of the phenylselenonyl group by iodide proceeded smoothly to furnish iodide derivative **I-242**, which was reduced (Raney Ni, H_2 , MeOH, RT) to methyl 2-ethyl phenylalanate **I-243** in 65% yield.[83]

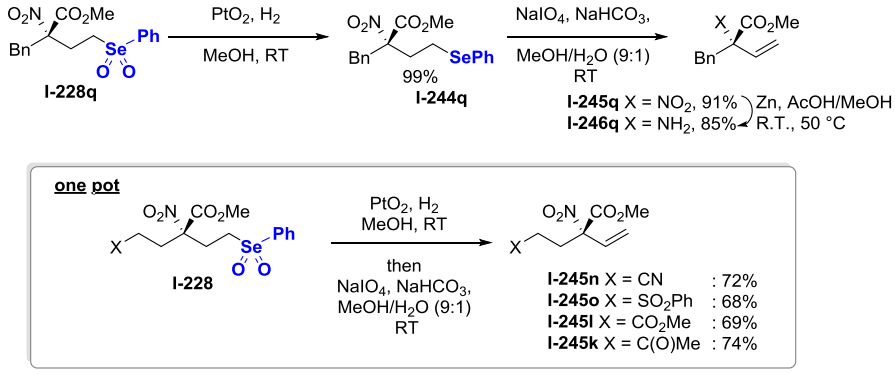
[80] K. B. Sharpless, R. F. Lauer, A. Y. Teranishi, *J. Am. Chem. Soc.* **1973**, *95*, 6137.
[81] A. Krief, W. Dumont, J.-N. Denis, *J. Chem. Soc., Chem. Commun.* **1985**, 571.
[82] Synthesis of racemic **I-241**, see: M. W. Holladay, A. M. Nadzan, *J. Org. Chem.* **1991**, *56*, 3900.
[83] Chiral auxiliary-based synthesis of enantio-enriched 12,see: a) M. Kolb, J. Barth, *Liebigs Ann. Chem.* **1983**, *1668*; b) A. Studer, D. Seebach, *Liebigs Ann.* **1995**, *217*; c) T. Satoh, M. Hirano, A. Kuroiwa, Y. Kaneko, *Tetrahedron* **2006**, *62*, 9268.



Scheme 62: Chemical transformations of the enantioenriched Michael adduct I-228q.

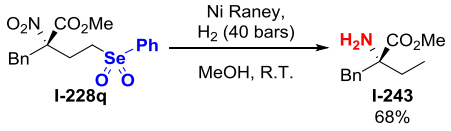
In the course of this study, different reductive conditions were explored to convert the nitro to amine. Unexpectively, hydrogenation of **I-228q** in the presence of Adam's catalyst reduced the phenyl selenone to phenyl selenide (confirmed by HRMS, ^{1}H, ^{13}C and ^{77}Se NMR) **I-244q** in a quantitative yield (Scheme 63). This new reaction, which was serendipitously discovered, is chemoselective to the phenylselenonyl group, the nitro group was stable under these conditions. To the best of our knowledge, there was only one example on the reduction of phenyl selenone to phenyl selenide (PI_3 , $CHCl_3$, 0 °C) accomplished in a simple substrate.[84] Treatment of **I-244q** with sodium periodate followed by Grieco elimination produced the vinyl substituted derivative **I-245q** in 95% yield. The reduction of the nitro group of the compound **I-245q** was possible with elemental Zn in a solution of AcOH/MeOH (1:1) at 50 °C and furnished then the methyl α-vinyl phenylalanate **I-246q**.[85] The conversion of **I-228q** to **I-245q** could be realized in a one-pot fashion in 91% yield. This one-pot process was compatible with a number of functions such as cyano, phenylsulfonyl, ester and carbonyl groups as illustrated by the successful synthesis of compounds **I-245n**, **I-245o**, **I-245l** and **I-245k**. We note that this two-steps sequence represented formally an enantioselective vinylation of an enolate. Inspite of the clear synthetic potentials, only few methods exist for accomplishing such transformation.[86]

[84] A. Krief, W. Dumont, J.-N. Denis, *J. Chem. Soc., Chem. Commun.* **1985**, 571.
[85] A multistep synthesis of enantio-enriched 15m using Seebach's diastereoseletive alkylation approach, see: A. Sacchetti, A. Silvani, G. Lesma, T. Pilati, *J. Org. Chem.* **2011**, *76*, 833.
[86] A. Chieffi, K. Kamikawa, J. Ahman, J. M. Fox, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 1897; T. B. Poulsen, L. Bernardi, M. Bell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, *45*, 6551; H. Kim, D. W. C. MacMillan, *J. Am.Chem. Soc.* **2008**, *130*, 398; A. M. Taylor, R. A. Altman, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 9900; S. Lou, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 5010; E. Skucas, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2012**, *134*, 9090; J. M. Stevens, D. W. C. MacMillan *J. Am. Chem. Soc.* **2013**, *135*, 11756.



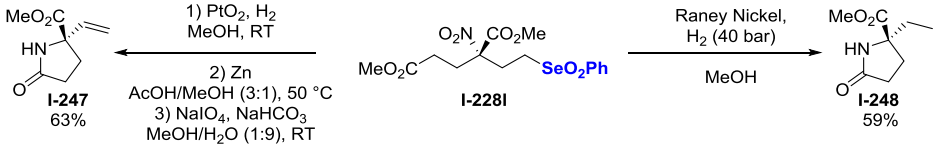
Scheme 63: chemoselective reduction of phenylselenonyl group - one pot reduction/oxidation sequence for the synthesis of enantioenriched vinyl derivative.

Reduction of **I-228q** with Raney nickel under 40 bars of H_2 in MeOH afforded directly the methyl 2-ethyl (R)-phenylalanate **I-243** in which both nitro and phenylselenonyl groups were reduced (Scheme6). This represented, to the best of our knowledge, the first example of reduction of alkyl phenylselenone to alkane.



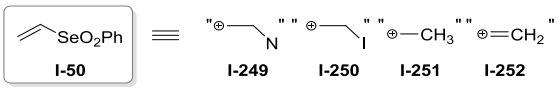
Scheme 64: Reduction of alkyl phenyl selenone to alkanes

Applying this protocol to **I-228l** allowed a one-pot synthesis of methyl (*R*)-2-ethyl pyroglutamate **I-248** by a reduction/lactamizaiton sequence. To further illustrate the versatility of our approach, compound **I-228l** was successfully converted to methyl (*S*)-2-vinylpyroglutamate **I-247** using the chemistry detailed in Scheme 63.We stressed that examples of quaternary α-amino acids (**I-241**, **I-243**, **I-246q**, **I-247**, **I-248**) presented herein are all difficultly accessible otherwise.



Scheme 65: Synthesis of enantioenriched γ-lactam

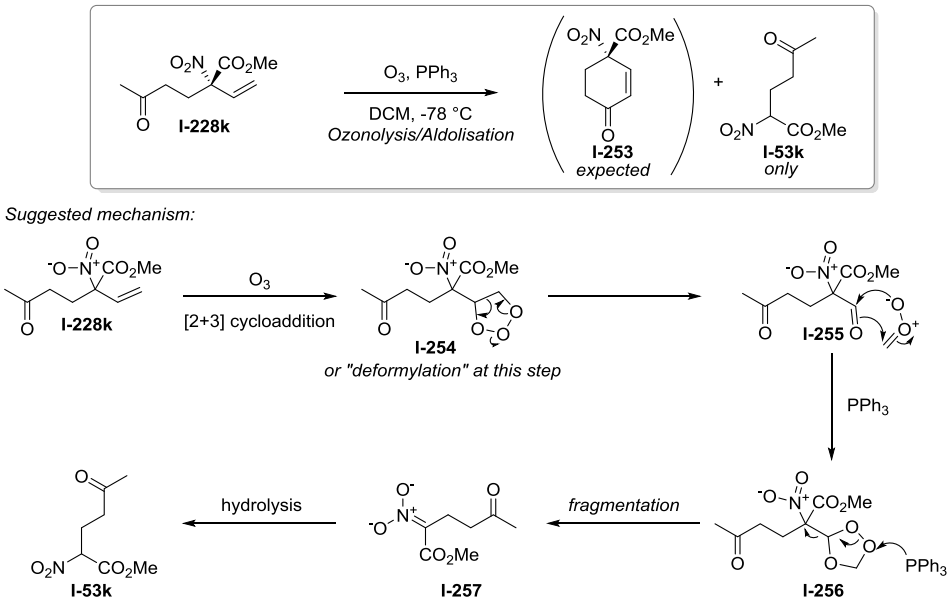
With all the transformations depicted previously, we could consider the phenyl vinyl selenone **I-50** as a synthetic equivalent of "+CH_2CH_2N", "+CH_2CH_2I", "+CH_2CH_3" and "+$CH{=}CH_2$". We believe that none of the other known Michael acceptors could be as versatile as phenyl vinyl selenone.



Scheme 66: phenyl vinyl selenone as a switchable synthetic synthon

Unexpected transformation:

The synthesis of other interesting building blocks has also been envisaged. The enantioenriched 4-ester-4-nitrocyclohex-2-en-1-one **I-253** could be a good example. The racemic version of this 6-membered ring has been made *via* Diels-Alder reaction using the Danishefsky diene.[87] The considered sequence was an ozonolysis/intramolecular aldolisation starting from **I-228k**. Unfortunatly, only methyl 2-nitro-5-oxohexanoate **I-53k** was isolated in 60% yield. Due to the presence of two electron-withdrawing groups in α position of the vinyl, the deformylation after ozonolysis was easy. To avoid this fragmentation, the preliminary reduction of the nitro to the amine could have been a solution.

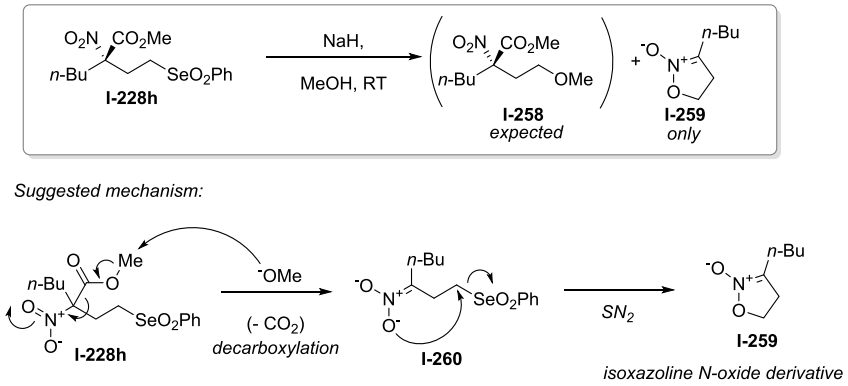


Scheme 67: Fragmentation of I-228k

In order to substitute the phenyl selenonyl group by an alkoxy group, sodium hydride was added to a solution of **I-228h** in methanol. Surprisingly, instead of the expected ether derivative **I-258** the isoxazoline *N*-oxide **I-259** was isolated. The formation of this compound could be rationalized by a decarboxylation of **I-228h** followed by the intramolecular displacing of the selenieted group with the nitro group to offer the 5-membered heterocycle **I-**

[87] A. Avenoza, J. I. Barriobero, C. Cativiela, M. A. Fernández-Recio, J. M. Peregrina, F. Rodríguez, *Tetrahedron*, **2001** , *57*, 2745.

259. The synthesis of isoxazoline *N*-oxyide **I-259** has been mostly described by [3+2] cycloaddition of olefin and nitronate.[88]

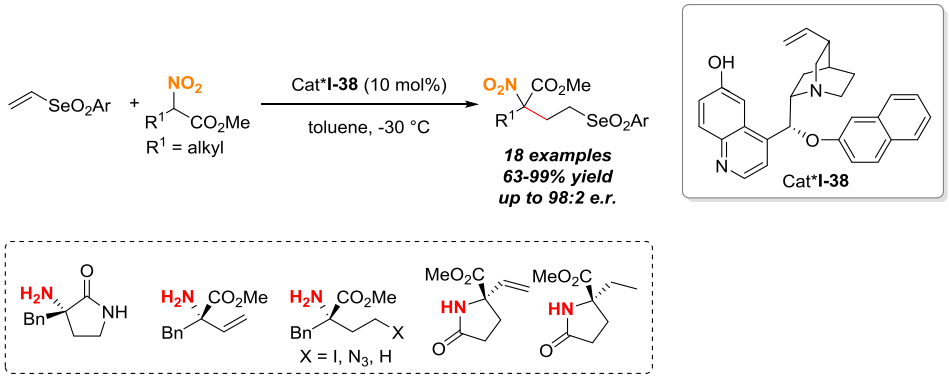


Scheme 68: Unexpected synthesis of isoxazoline *N*-oxide

[88] R. A. Kunetsky, A. D. Dilman, S. L. Ioffe, M. I Struchkova, Y. A. Strelenko, V. A. Tartakovsky, *Org. Lett.* **2003**, *5*, 4907.

Conclusion

The novel organocatalytic enantioselective Michael addition of α- substituted α-nitroacetate to phenyl vinyl selenone was successfully accomplished. The Michael adducts were isolated in good to excellent yields and enantioselectivities. The reaction was carried out in the presence of bifunctional *Cinchona alkaloid* derivative as organocatalyst. The resulting α,α-dialkyl α-nitroacetates were subsequently converted to cyclic and acyclic quaternary α–amino acids, taking advantage of the rich functionalities of these adducts. This methodology complements our previous work developed for the synthesis of α-aryl α-substituted isocyanoacetates. Novel protocols allowing chemoselective reduction of phenyl selenone to phenyl selenide and reduction of alkyl phenyl selenones to alkanes have also been reported. We believed that these chemoselective reductions would find applications in organic synthesis.[89]



Scheme 69: Development of Cinchona alkaloid-catalyzed enantioselective Michael addition of α-substituted nitroacetate to phenyl vinyl selenone

[89] A. Clemenceau, Q. Wang, J. Zhu, *Chem. Eur. J.* **2016**, *22*, 18368.

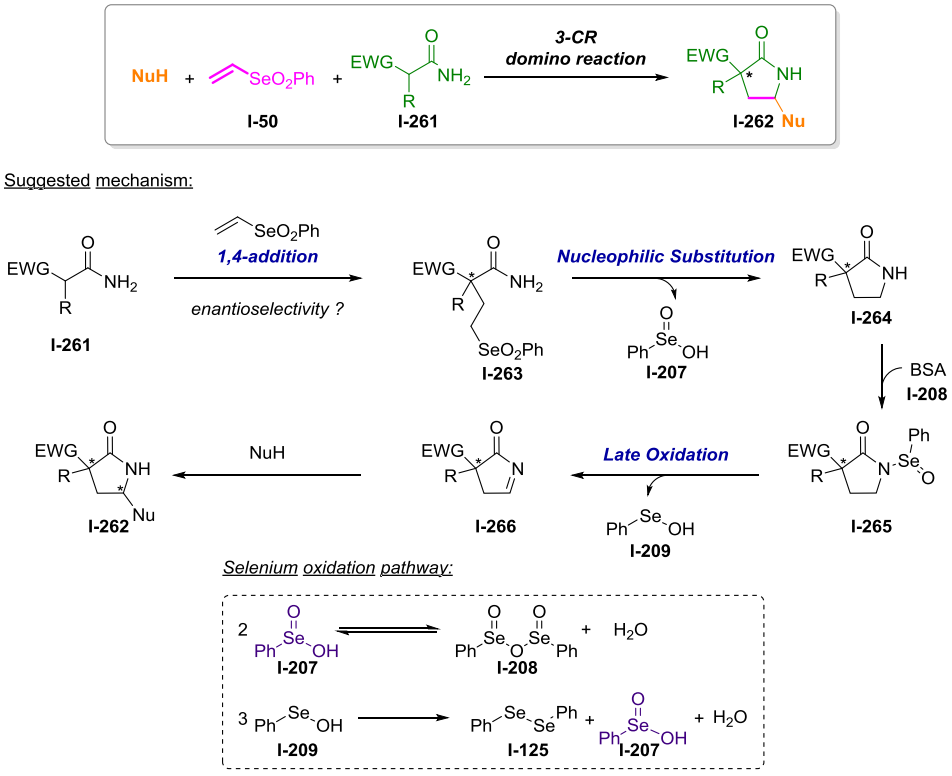
Chapter 2: α-Substituted α-Nitroacetamide as Michael Donor

Introduction

Preliminary idea

Interested by the triple role of the phenyl vinyl selenone (activator for conjugated addition, leaving group and oxidant) which have been highlighted in our group,[59] we imagined the synthesis of 5-membered ring derivatives using the phenyl selenonyl abilities in a multicomponent reaction where α-substituted α-electron-withdrawing amide **I-261**, phenyl vinyl selenone **I-50** and a nucleophile were reacting together (Scheme 70).

We hypothesized that the reaction of amide **I-261** with phenyl vinyl selenone would afford γ-lactam via a sequence of Michael addition and S_N2 displacement of phenyl selenonyl group by the amide nitrogen. Oxidation of amide by in situ generated BSA would provide N-acyl imine **I-266** which could be trapped by a nucleophile to give **I-262**.



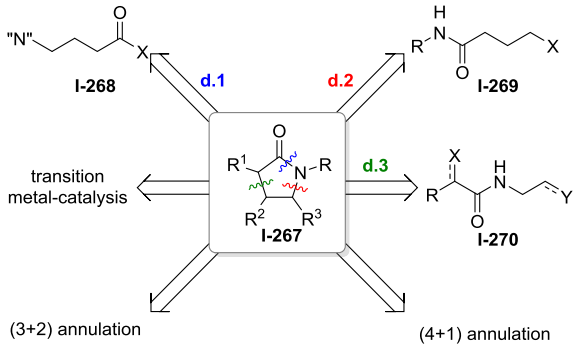
Scheme 70: Preliminary idea for the synthesis of γ-lactam

γ-Lactam synthesis

In the literature, the synthesis of γ-lactam **I-267** has been massively reported. This was not surprising; this 5-membered ring is present in many natural product, drugs and bioactive compounds which have shown to be important in medicinal chemistry.[90]

[90] J. Caruano, G. G. Muccioli, R. Robiette, *Org. Biomol. Chem.*, **2016**, *14*, 10134 and references cited therein.

Several way of synthetizing γ-lactam has been exploited using the classical bond disconnection between the carbonyl and the nitrogen atom (Scheme 71, **d.1**). With that, intramolecular peptide coupling with an amine and an activated carboxyl group or the reduction of amine mask (nitro, azide or imine) has been an easy method to make the 5-membered heterocycle. Cleaving the C-N bond could be also a good approach (Scheme 71, **d.2**).[91] This bond could be made by *N*-alkylation of γ-halide-amide.[92] The C-C bond disconnection **d.3** has also been envisaged to construct the cyclic 5-membered amide. Dieckmann condition, radical cyclization or even Grubbs metathesis have been possible by this way.[93]



Scheme 71: classical way for the synthesis γ-lactam synthesis

[4+1] Annulations, [3+2] annulations and also transition metal-catalyzed methodologies have been developed for the synthesis of γ-lactams. These approaches were less describes in the literature and have been a bit more detailed in this introduction.

[4+1] Annulation:

The [4+1] annulation has permited the construction of different *N*-protected 2-pyrrolidinone **I-272** by using the required primary amine **I-7** and 4-iodobutanoyl chloride **I-271** (Scheme 72, **(a)**).[94a] Fused 5-5 or 6-5 rings **I-275** could also be synthesized if amino

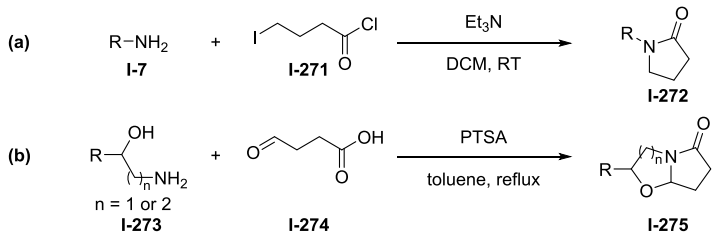
[91] (a) K. Shimamoto, M. Ishida, H. Shinozaki, Y. Ohfune, *J. Org. Chem.* **1991**, *56*, 4167; (b) D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13097 (c) J. J. W. Duan, L. Chen, Z. R. Wasserman, Z. Lu, R.-Q. Liu, M. B. Covington, M. Qian, K. D. Hardman, R. L. Magolda, R. C. Newton, D. D. Christ, R. R. Wexler, C. P. Decicco, *J. Med. Chem.* **2002**, *45*, 4954.

[92] (a) H. Ikuta, H. Shirota, S. Kobayashi, Y. Yamagishi, K. Yamada, I. Yamatsu, K. Katayama, *J. Med. Chem.* **1987**, *30*, 1995; (b) J. F. Kadow, D. M. Vyas, T. W. Doyle, *Tetrahedron Lett.* **1989**, *30*, 3299

[93] (a) E. Turos, J. E. Audia, S. J. Danishefsky, *J. Am. Chem. Soc.* **1989**, *111*, 8231; (b) T. Naito, Y. Honda, O. Miyata, I. Ninomiya, *Chem. Pharm. Bull.* **1993**, *41*, 217; (c) E. Choi, C. Lee, M. Cho, J. J. Seo, J. S. Yang, S. J. Oh, K. Lee, S.-K. Park, H. M. Kim, H. J. Kwon, G. Han, *J. Med. Chem.* **2012**, *55*, 10766.

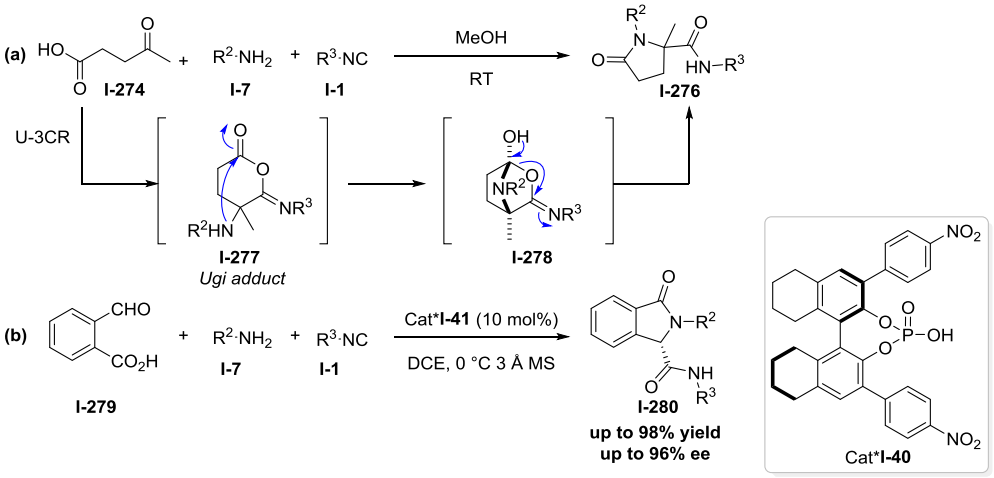
[94] 4+1 (a) acyl chloride and I: B. M. Kenda, A. C. Matagne, P. E. Talaga, P. M. Pasau, E. Differding, B. I. Lallemand, A. M. Frycia, F. G. Moureau, H. V. Klitgaard, M. R. Gillard, B. Fuks P. Michel, *J. Med. Chem.* **2004**, *47*, 530; (b) carboxylic acid and ketone: T. D. Aicher, B. Balkan, P. A. Bell, L. J. Brand, S. H. Cheon, R. O. Deems, J. B Fell, W. S. Fillers, J. D. Fraser, J. Gao, D. C. Knorr, G. G. Kahle, C. L. Leone, J. Nadelson, R. Simpson, H. C. Smith, *J. Med. Chem.* **1998**, 41, 4556.

alcohol **I-273** were used with 4-oxobutanoic acid **I-274** in the presence of PTSA in toluene at reflux (Scheme 72, **(b)**).[94b]



Scheme 72: [4+1] annulation for γ-lactam synthesis

Interestingly, the Ugi type three-component reaction using a primary amine **I-7**, an isocyanide **I-1** and the carboxylic acid **I-274** bearing a β-carbonyl group afforded also γ-lactam **I-276**.[95a] After the trapping of the reactive nitrilium intermediate by the internal carboxylate to afford the intermediate **I-277**, the intramolecular attack of the amine to the carboxyl group gave the bridged compound **I-278**. The fragmentation of the bridged system delivered finally the γ-lactam **I-276** (Scheme 73, **(a)**). Last year, an asymmetric version of this Ugi type reaction using 2-formylbenzoic acid **I-279** in the presence of Cat***I-40** as organocatalyst has been developed to produce enantioenriched 3-oxoisoindoline-1-carboxamides **I-270** (Scheme 73, **(b)**).[95b]

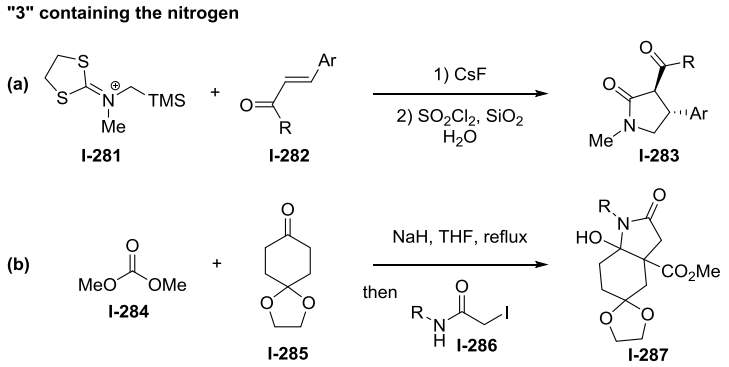


Scheme 73: Ugi type reaction for γ-lactam synthesis

[95] Ugi : (a) C. C. Musonda, J. Gut, P. J. Rosenthal, V. Yardley, R. C. Carvalho de Souza, K. Chibale, *Biorg. Med. Chem.* **2006**, *14*, 5605; (b) enantio: Y. Zhang, Y.-F. Ao, Z.-T. Huang, D.-X. Wang, M.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2016**, *55*, 5282.

[3+2] Annulation:

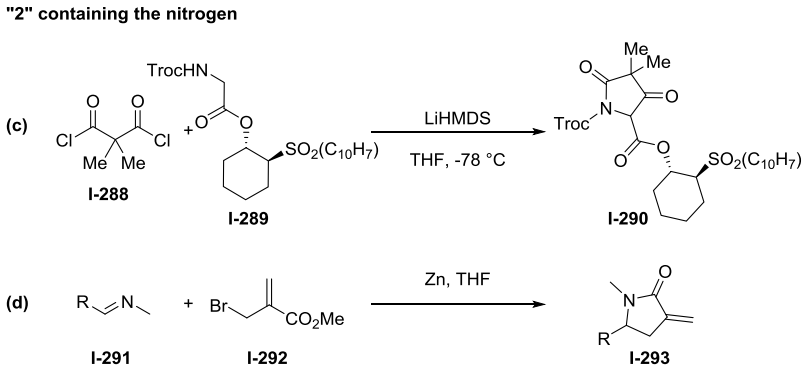
Different [3+2] annulations exist for the synthesis of this 5-membered heterocycle. The three-atoms unit containing the nitrogen could be played by azomethine ylide. After de-silylation of the ammonium salt **I-281**, the reactive azomethine ylide generated *in situ* reacted with electron poor dipolarophile **I-282** to afford, after the deprotection of the dithiolane, the γ-lactam **I-283** (Scheme 74, **(a)**).[96a] Three-atoms motif containing nitrogen such as 2-iodo-*N*-substituted acetamide **I-286** has been also a good partner in the [3+2] annulation. After generating the stabilized enolate of the ketone **I-285** with dimethyl carbonate **I-284** and sodium hydride, the 2-iodoacetamide **I-286** was added to the mixture to afford the fused lactam **I-287** (Scheme 74, **(b)**).[96b]



Scheme 74: [3+2] annulation γ-lactam synthesis with 3-atom unit containing nitrogen

Two-atoms partners containing nitrogen have also allowed the formation of γ-lactam. Shenvi and Corey described the diastereoselective synthesis of this kind of cyclic amide using a chiral glycine derivative **I-289** and dimethylmalonyl dichloride **I-288** for the total synthesis of (−)-7-methylomuralide (Scheme 75, **(c)**).[96c] Finally, the addition of an alkyl zinc bromide derivative to an imine, another two-atoms unit containing a nitrogen, followed by an intramolecular nucleophilic addition to the ester afforded the 3-methylenepyrrolidin-2-one derivative **I-293** (Scheme 75, **(d)**).[96d]

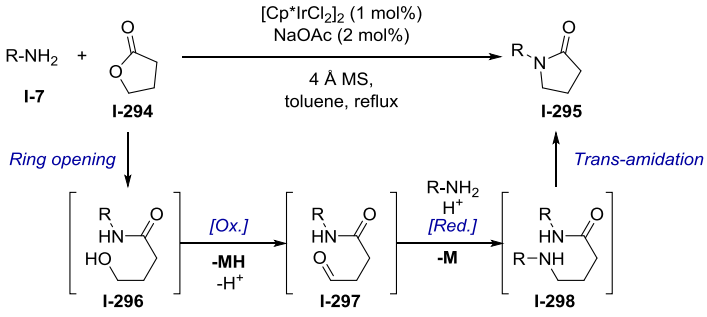
[96] C. W. G. Fishwick, R. J. Foster and R. E. Carr, *Tetrahedron Lett.* **1996**, *37*, 3915; (b) S. Gao, Y. Q. Tu, X. Hu, S. Wang, R. Hua, Y. Jiang, Y. Zhao, X. Fan and S. Zhang, *Org. Lett.* **2006**, *8*, 2373; (c) R. A. Shenvi and E. J. Corey, *J. Am. Chem. Soc.* **2009**, *131*, 5746; (d) A. Enz, D. Feuerbach, M. U. Frederiksen, C. Gentsch, K. Hurth, W. Müller, J. Nozulak and B. L. Roy, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1287.



Scheme 75: [3+2] annulation γ-lactam synthesis 2-atom unit containing nitrogen

Metal-catalyzed γ-lactam synthesis:

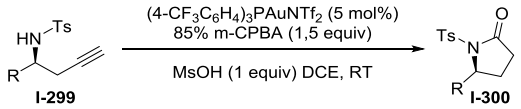
The design of specific metal-catalyzed reactions for the synthesis of γ-lactams have also been reported. Some transformations have been arbitrarily selected and depicted in the following schemes (Scheme 76, Scheme 77, Scheme 78). For example, the conversion of lactone **I-294** to lactam **I-295** has been described by Hong in 2015 using iridium complex and primary amine **I-7** (Scheme 76). In the suggested mechanism of this reaction, the ring opening of lactone **I-294** with a primary amine gave the linear hydroxyamide **I-296** which was oxidized by the iridium complex by hydrogen transfer to the 4-oxobutanamide **I-297**. This aldehyde was trapped by another molecule of primary amine **I-7** and reduced by the iridium complex to offer 4-aminobutanamide **I-298**. Finally the desired cyclic amide was formed after transamidation **I-295**.[97]



Scheme 76: Iridium-catalyzed γ-lactam synthesis

The synthesis of γ-lactam **I-300** was also possible using gold-catalyzed tandem cycloisomerization/oxidation on enantiopure homopropargylic sulfonamides **I-299** (Scheme 77).[98]

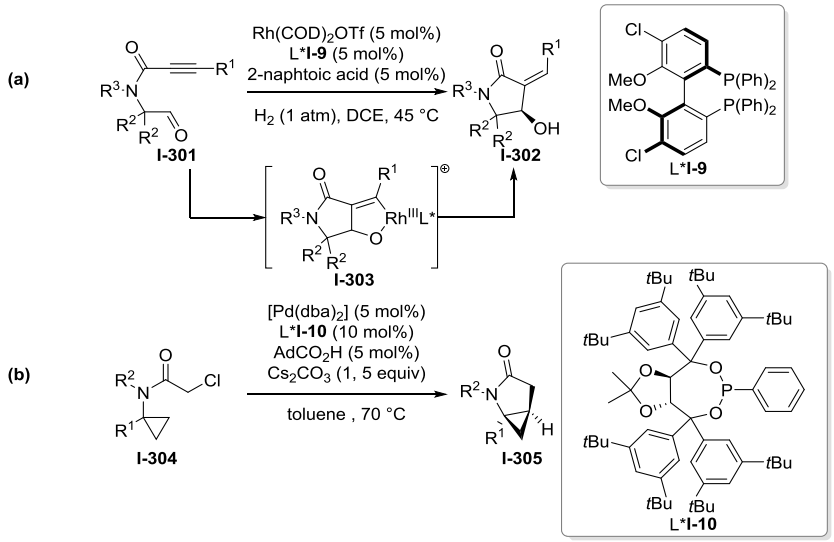
[97] K. Kim, S. H. Hong, *J. Org. Chem.* **2015**, *80*, 4152.
[98] C. Shu, M.-Q. Liu, S.-S. Wang, L. Li, L.-W. Ye, *J. Org. Chem.* **2013**, *78*, 3292.



Scheme 77: Gold-catalyzed γ-lactam synthesis

Enantioselective metal-catalyzed syntheses of chiral γ-lactam were also known (Scheme 78, **(a)** & **(b)**).[99] Krische has highlighted the asymmetric rhodium-catalyzed cyclization of acetylenic aldehydes **I-301** where a chiral diphosphine ligand L***I-9** coordinated to a rhodacycle intermediate **I-303** was involved and afforded after reductive cyclization the enantioenriched γ-lactam **I-302**. The palladium(0)-catalyzed C-H activation of cyclopropyl chloroacetamide **I-304** described by Cramer and Pedroni in 2015 permited also the access to enantioenriched pyrrolidines **I-305**. In this transformation where a $C(sp^3)$-$C(sp^3)$ bond formation was constructed, bulky TADDOL phosphonite ligand L***I-10** has been specially elaborated to induced high degree of chirality.

It is notable that for some of these metal-catalyzed γ-lactam syntheses, a well elaborated starting material was needed which could take, sometimes, several steps to be constructed.



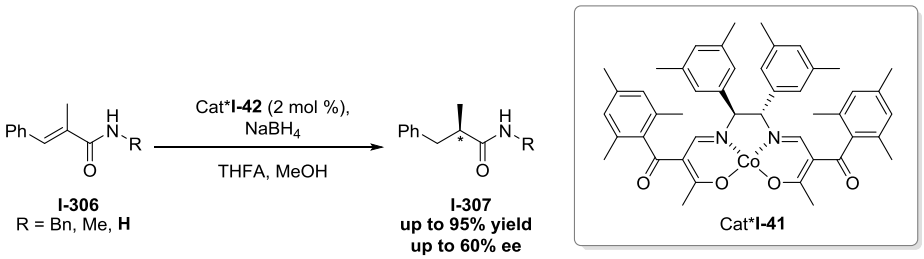
Scheme 78: enantioselective metal-catalyzed γ-lactam synthesis

[99] (a) J. U. Rhee, M. J. Krische, *J. Am. Chem. Soc.* **2006**, *128*, 10674; (b) J. Pedroni, N. Cramer, *Angew. Chem. Int. Ed.* **2015**, *54*, 11826.

Literature precedent with phenyl vinyl selenone and α-substituted α-electron withdrawing-amide

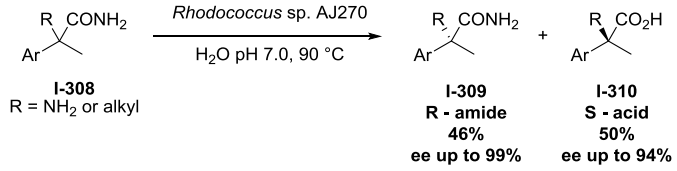
Only few example of asymmetric transformation using *N*-non protected amide have been developed by the scientific community. [18c,100] The difficulties encountered due to the relatively high pKa of the α-C-H, the possible deprotonation of the labile N-H proton and the multiple coordination site of the substrate for the chiral catalyst were the plausible arguments which rendered hard the induction of enantioselectivity.[18c]

In 2003, Yamada reported an enantioselective reduction of (*E*)-2-methyl-3-phenylacrylamide **I-306** using $NaBH_4$ and the cobalt complex Cat***I-41**. In this reaction primary and secondary unsaturated amide could be reduced albeit with a maximum of 60% of enantioselective excess (Scheme 79). [101]



Scheme 79: enantioselective 1,4-reduction of unsaturated primary amide

Enzymatic kinetic resolution appeared to be an excellent tool for the synthesis of enantiopure α,α-disubstituted amide. With amidase *Rhodococcus* sp. AJ270, enantiopure (*R*)-amides **I-309** could be separated from the highly enantioenriched (*S*)-carboxylic acid **I-310**. It was also important to note that is possible to convert cyano compound to enantioenriched amide derivative by using nitrile hydratase (Scheme 80).[102]

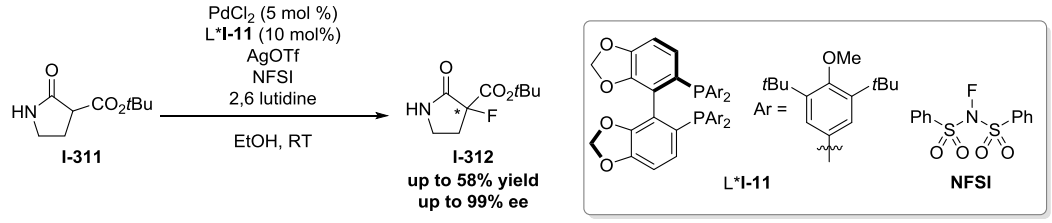


Scheme 80: Enzyme kinetic resolution

In 2007, the enantioselective α-fluorination of unprotected α-*tert*-butoxycarbonyl lactams **I-311** has been described by Sodoeka. The *in situ* formation of the chiral active complex was obtained when palladium chloride, chiral ligand L***I-11** and AgOTf were mixed

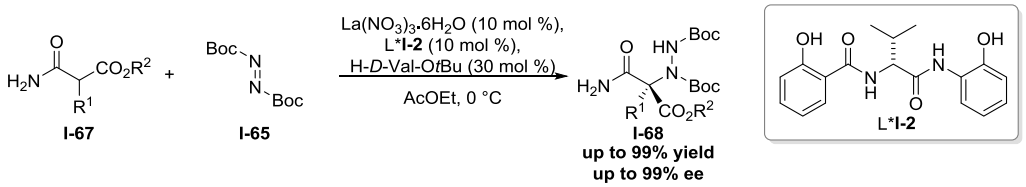
[100] Described in ref [18c]: α-CH proton pKa = 21.3 amide H trans: pKa = 27.8 H cis: pKa = 24.
[101] 1,4-reduction of unsaturated primary amide: Y. Ohtsuka, T. Ikeno, T. Yamada, *Tetrahedron: Asymmetry*, **2003**, *14*, 967.
[102] Enzymatic kinetic resolution of primary amides: M.-X. Wang, *Top. Catal.*, **2005**, *35*, 117, and references cited therein.

together which offered the fluorinated lactam **I-312** in 58% yield and excellent enantioselectivity if NFSI was used as fluorine source and 2,6-lutidine as base.[103]



Scheme 81: enantioselective α-fluorination of *N*-unprotected *tert*-butoxycarbonyl lactams

The use of *N*-unprotected amide have been also explored in diastereoselective transformations[104] but finally, the most relevant utilization has been described by Shibasaki and coworkers with the enantioselective electrophilic amination of α-substituted α-amidoacetate **I-67**. In this reaction, α-substituted α-amidoacetate **I-67** reacted with azodicarboxylate **I-65** in the presence of $La(NO_3)_3 \bullet 6H_2O$, the peptide-based ligand L***I-2** and O-*tert*butyl valine to give highly enantioenriched α-quaternary amide in excellent yield (Scheme 82).[18c105]



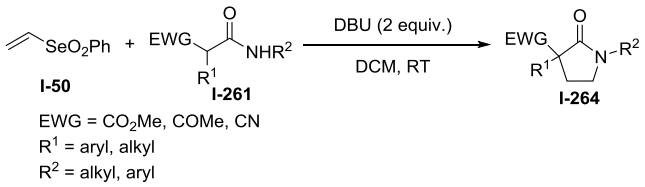
Scheme 82: enantioselective electrophilic amination for γ-lactam synthesis

Combination of phenyl vinyl selenone and amide

The combination of *N*-unprotected amide and phenyl vinyl selenone has already been described. It was in 2013 that Marini and coworkers reported the reaction between phenyl vinyl selenone and α-substituted α-electron-withdrawing acetamide **I-261** (α-substituted α-ketoacetamides, α-substituted α-malonylacetamides, or α-substituted α-cyanoacetamides) for the synthesis of *N*-protected α,α-disubstituted γ-lactam **I-264**. This racemic [3+2] annulation

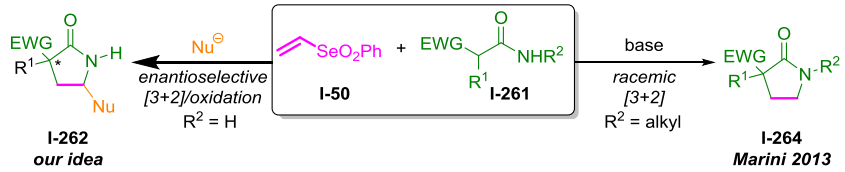
[103] For catalytic asymmetric fluorination: T. Suzuki, T. Oto, Y. Hamashima, M. Sodeoka, *J. Org. Chem.* **2007**, *72*, 246.
[104] Diastereoselective reactions using N-nonsubstituted R –alkoxycarbonyl amides as substrates, see: M. C. Kozlowski, E. S. DiVirgilio, K. Malolanarasimhan, C. A. Mulrooney, *Tetrahedron: Asymmetry* **2005**, *16*, 3599. Catalytic transformation utilizing N-nonsubstituted R -alkoxycarbonyl amides, see: J. Zhang, K. D. Sarma, T. T. Curran, D. T. Belmont, J. G. Davidson, *J. Org. Chem.* **2005**, *70*, 5890.
[105] F. Berhal, S. Takechi, N. Kumagai, M. Shibasaki, *Chem. Eur. J.* **2011**, *17*, 1915. Review: N. Kumagai, M. Shabasaki, *Angew. Chem. Int. Ed.* **2013**, *52*, 223.

between phenyl vinyl selenone **I-50** and secondary amides occurred in the presence of 2 equivalents of DBU in DCM at room temperature.[106]



Scheme 83: [3+2] annulation using phenyl vinyl selenone for the synthesis of γ-lactam.

Inspired by their approach, we decided to use phenyl vinyl selenone **I-50** and different α-substituted α-electron-withdrawing acetamides **I-261** in the hope of developing an enantioselective version of this transformation and a 3-component reaction exploiting the triple role of the phenyl vinyl selenone (Scheme 84).



Scheme 84: Our approach for the synthesis of enantioenriched γ-lactam

Results & Discussion

α-Substituted α-amidoacetate as starting material

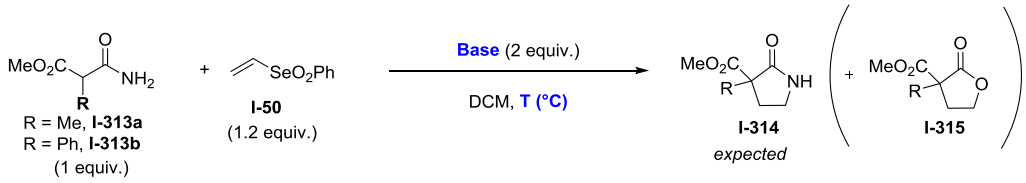
Brønsted base activation

To start the investigation, 2-substituted methyl 3-amino-3oxo-propanoate **I-313** and phenyl vinyl selenone **I-50** were used as test substrate and different bases were tried to promote the 1,4-nucleophilic addition. 2 equivalents of base, 1 equivalent of **I-313** and 1.2 equivalent of pheny vinyl selenone were mixed together in DCM (Table 7). If the α-substituent of the α-amidoacetate was a methyl (**I-313a**), Et_3N and *t*-BuOK lead to messy reactions. Traces of the desired lactam **I-314** were observed when NaH, DBU and Cs_2CO_3 were used. Surprisingly, the lactone **I-315** was isolated in 45% when TMG was used as strong organic base. In order to develop an enantioselective transformation, quinine Cat***I-18** was chosen as chiral organocatalyst. Unfortunately, only the starting materials were recovered. Methyl α-phenyl amidoacetate **I-313b** was also used as substrate to render the α-CH proton more acidic. With 2 equivalents of NaH, the reaction was messy. In the presence of 2 equivalents of KOH the formation of lactam **I-314** was possible in 25% yield but the lactone

[106] S. Sternativo, B. Battistelli, L. Bagnoli, C. Santi, L. Testaferri, F. Marini, *Tetrahedron Lett.* **2013**, *54*, 6755.

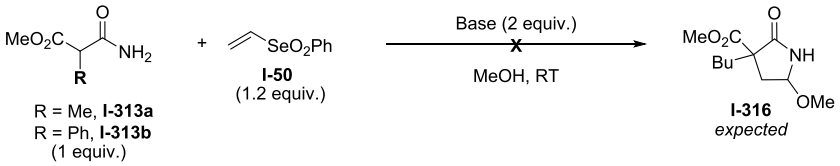
I-315 was also formed in 40% NMR yield. Reducing the amount of base to 1.3 equivalent lead, in the case of NaH, to the formation of 40% of lactam **I-314** and 45% of lactone **I-315**. With KOH, the reaction was complicated and only trace amount of lactone **I-315** were detected.

Table 7: Brønsted base screening.



Entry	R	Base	Temperature	Observation
1	**I-313a**	Et_3N	RT, 40 °C	Messy reaction
2	**I-313a**	NaH	RT, 40 °C	Messy, traces of **I-314**
3	**I-313a**	Cs_2CO_3	RT, 40 °C	Messy, traces of **I-314**
4	**I-313a**	*t*-BuOK	RT, 40 °C	Messy reaction
5	**I-313a**	DBU	RT	Messy, traces of **I-314**
6	**I-313a**	TMG	RT	45% of **I-315**
7	**I-313a**	quinine	RT, 40 °C	No reaction
8	**I-313b**	NaH	RT	Messy reaction
9	**I-313b**	KOH	RT	20% yield of **I-314** + 30% yield of **I-315**
10	**I-313b**	NaH (1.3 equiv)	RT	30% yield of **I-314** + 35% yield of **I-315**
11	**I-313b**	KOH (1.3 equiv)	RT	trace of **I-315**
12	**I-313b**	Quinine (Cat***I-18**)	RT	No reaction

Methanol was used as solvent with the expectation that methanol could play the external nucleophile for the formation of the 3-CR adduct **I-316**. However, by changing the base, (Et_3N, NaH or KOH), the α-substituent (R = Me or Ph), only messy reaction were observed (Scheme 85).



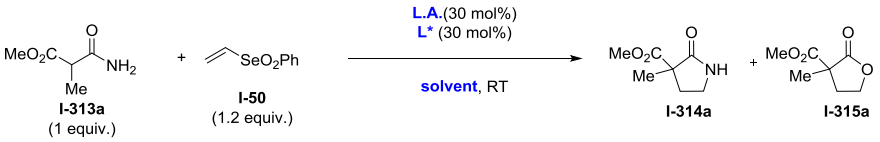
Scheme 85: MeOH as solvent and partner in the 3-CR.

Lewis acid activation

When the nitrogen of the amide is playing the nucleophile the lactam is formed whereas if the oxygen attack the phenyl selenonyl group, the cyclic imidate is formed which afford, after hydrolysis the lactone. Due to poor results obtained with Brønsted base we decided to utilize Lewis acids as catalyst. Excited by the enantioselective reaction described by Shibasaki and coworkers where rare earth metal complexes were used as catalyst system,[18c] we decided to explore this approach.

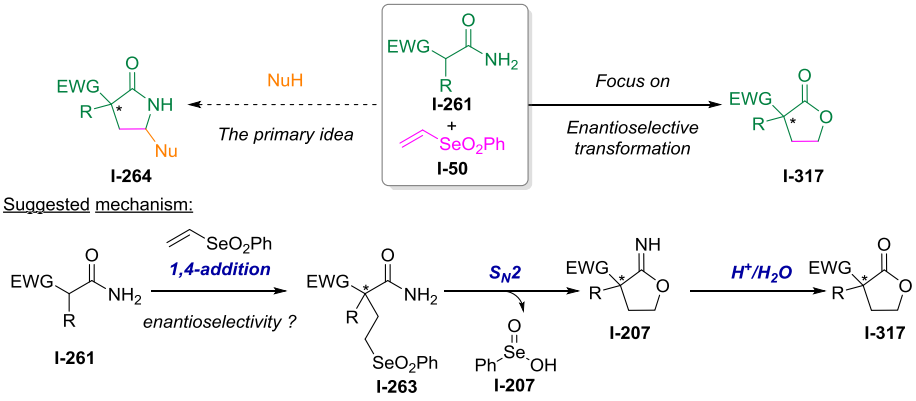
Different Lewis acids and ligands were screened (Table 8). When 30 mol% of $La(OTf)_3$, $La(NO_3)_3.6H_2O$, $GaBr_3$, $Er(OTf)_3$ or $EuCl_3$ were used respectively with 30 mol% of terpyridine, the formation of lactone **I-315a** was obtained. The best result was obtained with $La(OTf)_3$ (30 mol%), terpyridine (30 mol%), in toluene at RT leading to 48% NMR yield of the lactone **I-315a**. $LaBr_3$, $FeBr_3$ and $YbCl_3$ (entry 3, 5 and 7) however, were not able to promote the 1,4-addition. The presence of a Lewis acid was mandatory has shown in entry 9. Shibasaki's condition were also used (entry 10) but failed to catalyze this transformation.

Table 8: Lewis acid screening.



Entry	Conditions	Observation
1	$La(OTf)_3$ terpyridine, toluene	**I-315a** (48% NMR yield)
2	$La(NO_3)_3.6H_2O$ terpyridine, toluene	55% conv. in **I-315a (**28% yield)
3	$LaBr_3$, terpyridine, toluene	No reaction
4	$GaBr_3$, terpyridine, toluene	Full conv. in **I-315a** (42% yield)
5	$FeBr_3$, terpyridine, toluene, R.T. to 40 °C	No reaction
6	$Er(OTf)_3$, terpyridine, toluene	Full conv. in **I-315a** (48% yield)
7	$YbCl_3$, terpyridine, toluene, R.T. to 40 °C	No reaction
8	$EuCl_3$, terpyridine, toluene R.T.	67% conv. in **I-315a** (17% yield)
9	No L.A., terpyridine, toluene R.T. to 40 °C	No reaction
10	$La(NO_3)_3.6H_2O$, L***I-2**, H-*D*-Val-OtBu, AcOEt,	No reaction

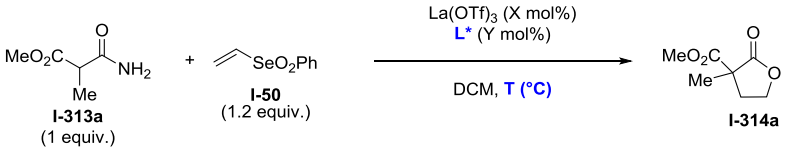
$La(OTf)_3$ seems to be the most promising Lewis acid to catalyse the formation of the lactone **I-315a** even if moderate yield was obtained. Therefore, we decided to modify our preliminary idea which was the synthesis of α,α–disubstituted γ–lactam and focused on the enantioselective synthesis α,α–disubstituted γ–lactone **I-317** (Scheme 86).



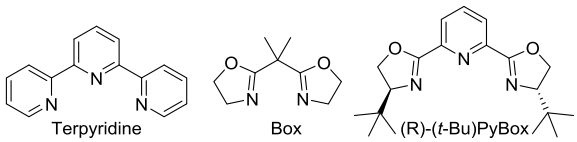
Scheme 86: Enantioselective lactone synthesis.

After a preliminary screening of different parameters (ratio Lewis acid/ligand, ligand and temperature) using $La(OTf)_3$ as Lewis acid, the best conditions to form the lactone **I-314a** were with 30 mol% of terpyridine as ligand, 30 mol% of Lewis acid at room temperature in DCM (Table 9). Under these conditions **I-314a** was obtained in 48% yield.

Table 9: Condition screening when $La(OTf)_3$ is used as Lewis acid.

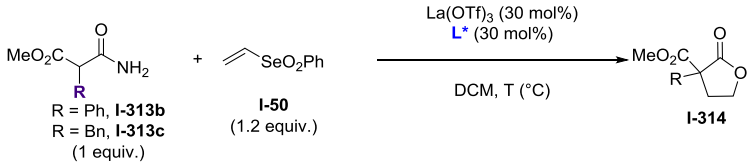


Entry	Ratio Lewis acid/Ligand (X:Y)	Ligand	Temperature	Observation
1	1 :1 (30 :30 mol%)	L**I-12**	R.T.	48% NMR yield
2	1 :0 (30 :0 mol%)	None	R.T.	44% NMR yield
3	1 :1 (30 :30 mol%)	L**I-13**	R.T.	36% NMR yield
4	1 :1 (30 :30 mol%)	L***I-14**	R.T.	25% NMR yield
5	1 :1 (100 :100 mol%)	L**I-12**	R.T.	12% NMR yield
6	1 :2 (30 :60 mol%)	L**I-12**	R.T.	46% NMR yield
7	1 :3 (30 :90 mol%)	L**I-12**	R.T.	46% NMR yield
8	2 :1 (30 :15 mol%)	L**I-12**	R.T.	36% NMR yield
9	1 :1 (30 :30 mol%)	L**I-12**	-40 °C	No reaction
10	1 :1 (30 :30 mol%)	L**I-12**	-20 °C	No reaction
11	1 :1 (30 :30 mol%)	L**I-12**	0 °C	45% Conv., 29% NMR yield

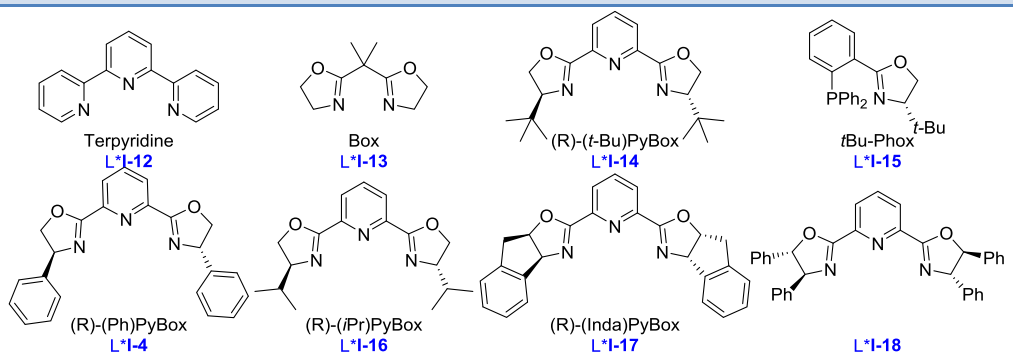


To render the reaction enantioselective, bis(oxazoline)pyridine derivatives, a class of chiral tridentate ligand, have been studied (Table 10). The α-substituted amidoacetate was replaced by methyl α-benzyl α-amidoacetate **I-313c** which was more easily separable and gave a greater UV signal strength on chiral SFC. When the reaction was run at room temperature, the conversion was very slow (Entries 1 to 6). The reaction was then heated to 40 °C and (Inda)pyBox and (*t*Bu)pyBox afforded the lactone **I-314c** in low yield and low enantioselectivity (Entries 8 and 9). The methyl α-phenyl amidoacetate **I-313b** was also used as starting material for this enantioselective Michael addition, however, low yield and *er* where obtained in this transformation (Entries 10 to 15). L***I-17** and L***I-18** allowed the formation of the lactone **I-314c** (64:36 *er*, 24% yield and 72:28, 20% yield respectively). The yields were low and the rest of the starting material was not converted to the desired product even after 72h of reaction time.

Table 10: Chiral ligand screening.



Entry	R	Ligand	T °C	yield	*er*
1	R = Bn	L***I-12**	R.T.	20% NMR yield	-
2	R = Bn	L***I-13**	R.T.	11% NMR yield	-
3	R = Bn	L***I-16**	R.T.	No reaction	-
4	R = Bn	L***I-4**	R.T.	No reaction	-
5	R = Bn	L***I-17**	R.T.	Low conversion	-
6	R = Bn	L***I-14**	R.T.	Low conversion	-
7	R = Bn	None	40 °C	No reaction	-
8	R = Bn	L***I-17**	40 °C	20% yield	55:45
9	R = Bn	L***I-14**	40 °C	20% yield	66:34
10	R = Ph	L***I-16**	40 °C	19% yield	55:45
11	R = Ph	L***I-4**	40 °C	26% yield	64:36
12	R = Ph	L***I-17**	40 °C	24% yield	54:46
13	R = Ph	L***I-14**	40 °C	17% yield	54:46
14	R = Ph	L***I-15**	40 °C	10% yield	52:48
15	R = Ph	L***I-18**	40 °C	20% yield	72:28

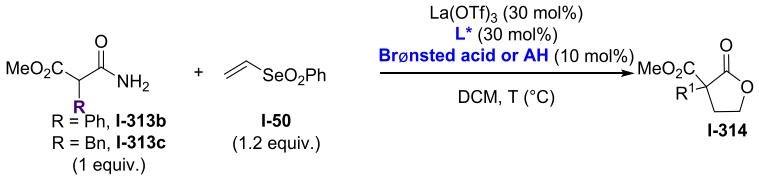


Brønsted acid activation & dual catalysis

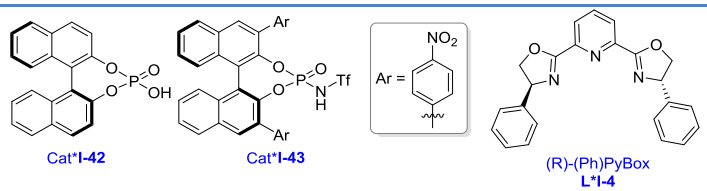
Brønsted acids have also been explored to develop this enantioselective reaction (Table 11). Unfortunately, 10 mol% of phosphoric acid Cat***I-42** or sulfonyl phosphoramide Cat***I-43** at room temperature or at 60 °C was not promoting the transformation (Entry 1 to 4).

The dual catalysis approach has been tried. By mixing a Lewis acid, a ligand and a Brønsted acid, several powerful reactions have been reported.[107] When $La(OTf)_3$, ligand L***I-4** and TFA were used together, no reaction was observed even at 60 °C. Finally, in the presence of lanthanim complex and Cat***I-42** or Cat***I-43** at 60 °C, the lactone **I-314b** was formed albeit with low yields and enantioselectivities (36-38% yield & 60:40 *er*).

Table 11: Brønsted acid screening.



Entry	R	T (°C)	Acid (10 mol%)	Lewis Acid/Ligand	Observation
1	R = Ph	R.T., 60 °C	Cat***I-42**	None	No reaction
2	R = Ph	R.T., 60 °C	Cat***I-43**	None	No reaction
3	R = Bn	R.T., 60 °C	Cat***I-42**	None	No reaction
4	R = Bn	R.T., 60 °C	Cat***I-43**	None	No reaction
5	R = Ph	R.T.	TFA	$La(OTf)_3$, L***I-4** (1:1)	No reaction
6	R = Ph	R.T.	Cat***I-42**	$La(OTf)_3$, L***I-4** (1:1)	No reaction
7	R = Ph	R.T.	Cat***I-43**	$La(OTf)_3$, L***I-4** (1:1)	No reaction
8	R = Ph	60 °C	TFA	$La(OTf)_3$, L***I-4** (1:1)	No reaction
9	R = Ph	60 °C	Cat***I-42**	$La(OTf)_3$, L***I-4** (1:1)	35% conv., 60:40 *er*
10	R = Ph	60 °C	Cat***I-43**	$La(OTf)_3$, L***I-4** (1:1)	38% conv., 61:39 *er*



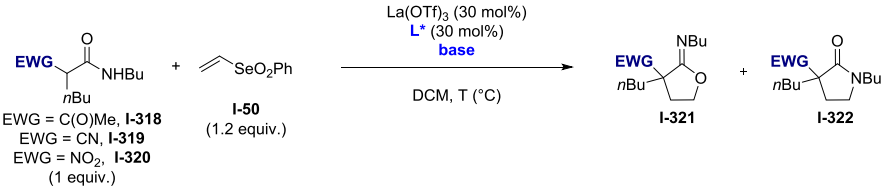
[107] M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem. Int. Ed.* **2007**, *46*, 6903. Review on metal catalysis + organocatalysis, see: Z. Du, Z. Shao *Chem. Soc. Rev.* **2013**, *42*, 1337.

Other α-substituted α-(electron-withdrawing)acetamide

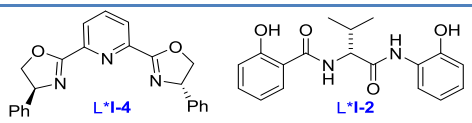
With these unfruitful results, we decided to replace the α-substituted α-amidoacetate by other α-substituted α-(electron-withdrawing) acetamides which could have a better affinity with the catalyst and a better reactivity. Therefore, we decided to change the ester group to carbonyl (**I-318**), cyano (**I-319**) or nitro (**I-320**) group on the Michael donor in this reaction.

Each of the three different α-(electron-withdrawing)acetamides were used separately with lanthanum-ligand complexes (Table 12). The $La(OTf)_3$-pyBox system or Shibasaki's complex gave no reaction for the three Michael donors even if the reaction was heated to 60 °C. When trimethylamine was added in the reaction, degradation of α-butyl α-ketoacetamide **I-318**, was observed. In the case of α-butyl α-cyanoacetamide **I-319**, a trace amount of the imidate **I-321** was detected. Nonetheless, the presence of an organic base with α-butyl α-nitroacetamide **I-320** allowed the full conversion of the starting material to the imidate **I-321** in 81% yield.

Table 12: Screening of other electron-withdrawing group on the starting material.



Entry	EWG	Ligand	Temperature	Base	Observation
1	C(O)Me	**L*I-4**	R.T., 60 °C	None	No reaction
2	C(O)Me	L***I-2**	R.T., 60 °C	None	No reaction
3	C(O)Me	**L*I-4**	R.T.	Et_3N	Degradation
4	C(O)Me	L***I-2**	R.T.	Et_3N	Degradation
5	CN	**L*I-4**	R.T., 60 °C	None	No reaction
6	CN	L***I-2**	R.T., 60 °C	None	No reaction
7	CN	**L*I-4**	R.T.	Et_3N	Trace of **I-321**
8	CN	L***I-2**	R.T.	Et_3N	Trace of **I-321**
9	NO_2	**L*I-4**	R.T., 60 °C	None	Trace of the imidate at 60 °C
10	NO_2	L***I-2**	R.T., 60 °C	None	No reaction
11	NO_2	**L*I-4**	R.T.	Et_3N	Full conv. to **I-321,** 81% yield
12	NO_2	L***I-2**	R.T.	Et_3N	Full conv. to **I-321**



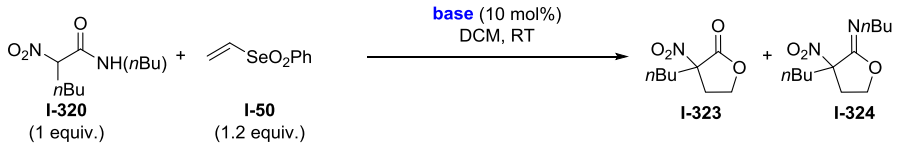
With the high yield obtained for the synthesis of the imidate **I-321** when the α-electron withdrawing group was a nitro group, we focused our investigation on α-substituted α-nitroacetamide **I-320** as substrate.

α-Substituted α-nitroacetamide as partner of choice

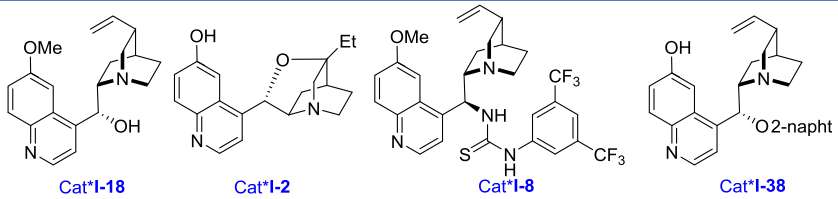
The first test reactions with α-substituted α-nitroacetamide **I-320** were performed in the presence of Brønsted base. To discriminate the presence of $La(OTf)_3$ or ligand; the reaction was run without the rare earth-ligand complex. Indeed, when trimethylamine was used as organic base, the Michael addition occurred to afford a mixture of imidate/lactone. It was interesting to note that the imidate was stable in this condition whereas previously the imidate was fully hydrolyzed to lactone. It appeared also that quinine Cat***I-18**, β-isocupreidine Cat***I-2**, thiourea derivative Cat***I-8** and Cat***I-38** triggered also the Michael addition/S_N2 sequence. The conversion of the starting material to the product was good but

the enantioselectivity of this transformation could not be recorded. Effectively, the product was not UV active and the UV detector of the SFC could not detect the lactone **I-323** as well as the imidate **I-324**.

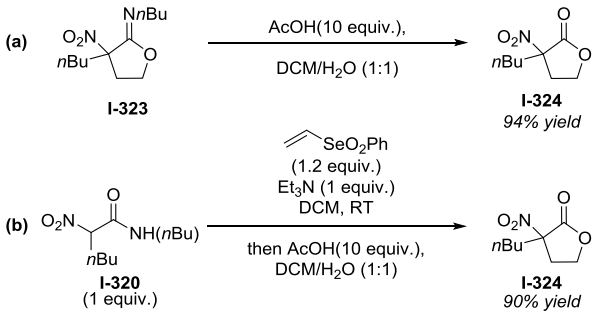
Table 13: Base screening.



Entry	Catalyst	lactone/imidate ratio	Isolated yield of lactone
1	Et_3N	10:90	78%
2	Cat***I-18**	45:55	35%
3	Cat***I-2**	16:84	59%
4	Cat***I-8**	35:65	57%
5	Cat***I-38**	50:50	47%



In order to fully convert the imidate **I-324** to the lactone **I-323**, we tried several hydrolysis conditions on the cyclic imidate **I-324**. The best result was obtained when acetic acid was added to a solution of **I-324** in a (1:1) mixture of DCM and water at room temperature. The desired cyclic compound **I-323** was isolated in 94% isolated yield (Scheme 87, **(a)**). A one pot synthesis combining the [3+2] annulation and the imidate hydrolysis has been also developed to give **I-323** in 90% yield (Scheme 87, **(b)**).

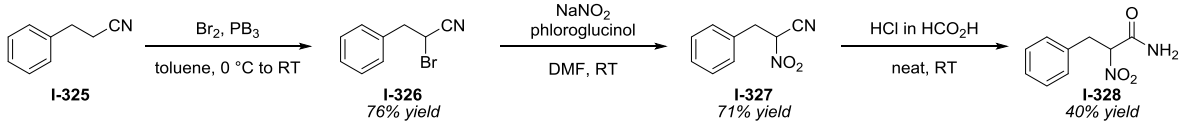


Scheme 87: Imidate hydrolysis to lactone.

To measure the enantioselective ratio of the reaction, other α-substituted α-nitroacetamides containing aromatic group for a better UV signal strength needed to be

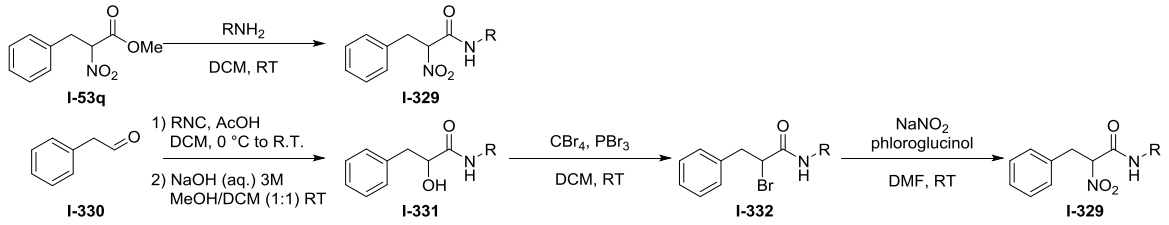
elaborated. To reach this goal, the unprecedented syntheses of primary, secondary and tertiary α-substituted α-nitroacetamides have been developed.

The primary amide **I-328** has been synthesized by α-bromination of 3-phenylpropanenitrile **I-325** followed by S_N2 with sodium nitrate and hydrolysis of the nitrile to the amide **I-328** in 22% yield over three steps.



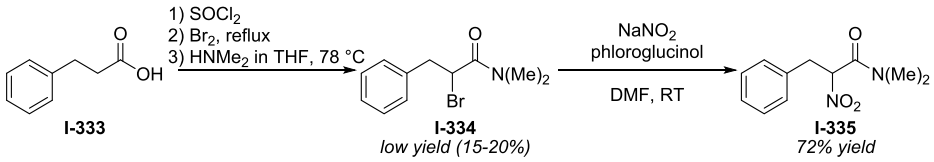
Scheme 88: Primary amide synthesis.

For the secondary amides **I-329**, the first approach envisaged was the transamidation of α-benzyl α-nitroacetate **I-53q** with primary amine **I-57**. This reaction gave good yield only in the case of not bulky primary amine. The other approach for the synthesis of **I-329** started with the Passerini 3-CR of 2-phenylacetaldehyde **I-330**, isonitrile **I-1** and acetic acid which afforded after deprotection the *N*-substituted α-benzyl α-hydroxyacetamide **I-331**. By continuing the sequence with an Appel reaction and a nucleophilic substitution, the secondary α-nitroacetamide **I-329** could be generally isolated in moderate to good yield.



Scheme 89: Secondary amide synthesis.

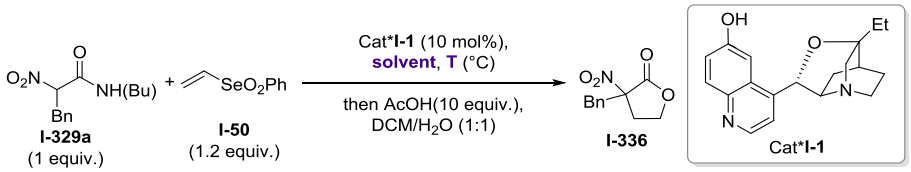
Finally, the tertiary amide was synthesized from 3-phenylpropanoic acid **I-333** by a one pot sequence acyl chloride formation/α-bromination/nucleophilic addition of *N*,*N*-dimethylamine sequence to deliver **I-334** in low yield. The final S_N2 with sodium nitrate offered the α-nitroacetamide **I-335** in 72% yield.



Scheme 90: Tertiary amide synthesis.

With this various amides in hands, we decided to use *N*-butyl α-benzyl α-nitroacetamide **I-329a** as model substrate and Cat***I-1** as organocatalyst. After screening the solvent and the temperature, we observed that all the solvent gave good yields and the temperature was not influencing the *er* with DCM as solvent. It was notable that toluene gave the best result with 90% yield and 60:40 *er* for **I-336** (Table 14).

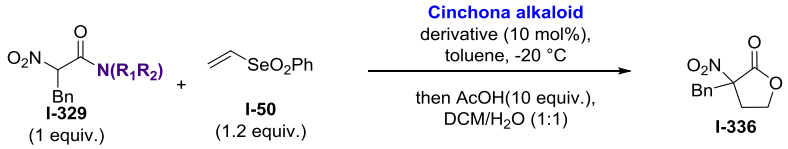
Table 14: Solvent screening.



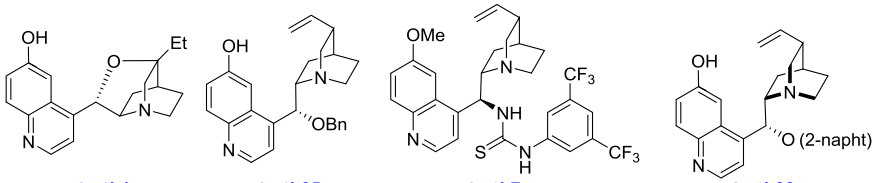
Entry	solvent	T (°C)	yield	*er*
1	DCM	R.T.	94%	50:50
2	DCM	-40 °C	92%	50:50
3	AcOEt	R.T.	87%	51:49
4	**Toluene**	R.T.	90%	**60:40**
5	THF	R.T.	91%	53:47
6	MeCN	R.T.	88%	58:42

The influence of the *N*-substituents of the amide was then studied (Table 15). Cat***I-1**, Cat***I-35** and Cat***I-7** were selected as organocatalyst for a preliminary screening due to the difference of chiral environment and H-bond donors. When *N*-unsubstituted amide **I-328** was utilized as substrate, moderate yield and low *er* were observed (Entry 1 & 2). Moreover, no reaction has been detected when Cat***I-7** is the catalyst (Entry 3). The tertiary amide **I-335** also gave poor result. Only no reaction or low yield/*er* were obtained (Entry 4 to 6). When secondary amides were used, the convertion toward the lactone was excellent and isolated yields were very good. For the enantioselectivity, moderate *er* (around 60:40) were obtained with **I-329a (**R = *n*-Bu) (Entry 7 to 9). The nitroacetamide **I-329b (**R = *t*-Bu) however gave interesting outcome with Cat***I-35** and Cat***I-7** (64:36 *er* and 61:39 *er* respectively) (Entry 11 & 12). *N*-(2,6-(dimethyl)phenyl) secondary amide **I-329c** was used but low induction where observed with the three selected catalysts (Entry 13 to 15). Surprisingly, we also observed that the best catalyst Cat***I-38** developed for the previous methodology gave poor enantioselectivety regardless of the nature of the *N*-substituent (Entry 16 to 19).

Table 15: *N*-Substitients screening.

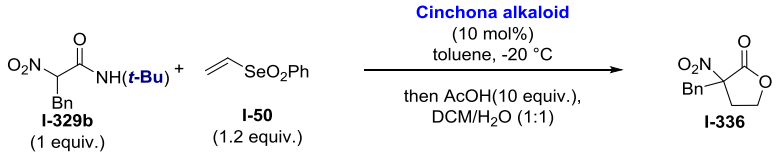


Entry	-N(R^1R^2)	Catalyst	Isolated Yield	*er*
1	-NH_2 (**I-328**)	Cat***I-1**	50%	51:49
2	-NH_2 (**I-328**)	Cat***I-35**	65%	51:49
3	-NH_2 (**I-328**)	Cat***I-7**	No reaction	-
4	-$N(Me)_2$ (**I-335**)	Cat***I-1**	25%	52:48
5	-$N(Me)_2$ (**I-335**)	Cat***I-35**	No reaction	-
6	-$N(Me)_2$ (**I-335**)	Cat***I-7**	No reaction	-
7	-NH(*n*-Bu) (**I-329a**)	Cat***I-1**	90%.	60:40
8	-NH(*n*-Bu) (**I-329a**)	Cat***I-35**	91%	60:40
9	-NH(*n*-Bu) (**I-329a**)	Cat***I-7**	89%	59:41
10	-NH(*t*-Bu) (**I-329b**)	Cat***I-1**	94%	55:45
11	-NH(*t*-Bu) (**I-329b**)	Cat***I-35**	92%	64:36
12	-NH(*t*-Bu) (**I-329b**)	Cat***I-7**	95%	61:39
13	-NH(*m*-xyl) (**I-329c**)	Cat***I-1**	93%	55:45
14	-NH(m-xyl) (**I-329c**)	Cat***I-35**	94%	59:41
15	-NH(*m*-xyl) (**I-329c**)	Cat***I-7**	92%	56:44
16	-NH(*n*-Bu) (**I-329a**)	Cat***I-38**	89%	55:45
17	-NH(*t*Bu) (**I-329b**)	Cat***I-38**	88%	53:47
18	-NH(Bn) (**I-329d**)	Cat***I-38**	91%	54:46
19	-NH(Me) (**I-329e**)	Cat***I-38**	87%	54:46

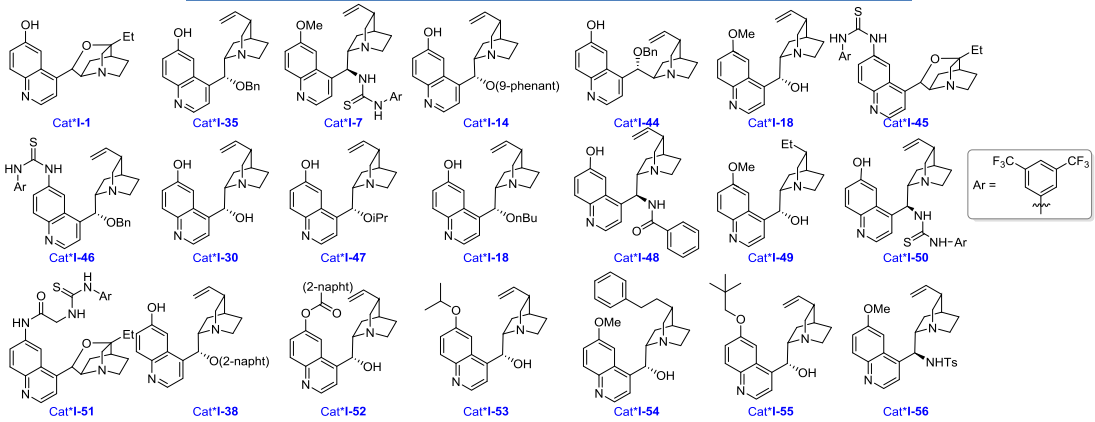


Because *N*-*t*-butyl secondary amide **I-329b** gave best results in our preliminary screening, further organocatalysts were tried using this structure (Table 16). To summarize this large screening of organocatalyst, the yields observed for the transformation were good for almost all the catalysts, only Cat***I-45** could not promote the reaction (Entry 8). The enantioselectivity ratio oscillates around 60:40 but the catalysts which possessed a free OH on C_9 gave the most interesting enantioselectivity (Entry 6, entry 13, entry 18 and entry 19). Notably, Cat***I-49** where the C_9 was OH and $C_{6'}$ was O*i*Pr afforded the best enantioselective ratio of 71:29 (entry 18). Other modification around the double bond or the use of other H-bond donor on $C_{6'}$ or C_9 of the organocatalyst did not lead to good chiral induction.

Table 16: *Cinchona alkaloid* screening.

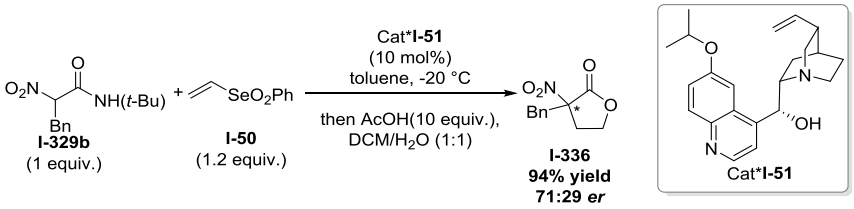


Entry	Catalyst	Isolated yield	*er*
1*	Cat***I-1**	94%	55:45
2*	Cat***I-35**	92%	64:36
3*	Cat***I-7**	95%	61:39
4	Cat***I-14**	80%	52:48
5	Cat***I-44**	92%	59:41
6	Cat***I-18**	85%	67:33
7	Cat***I-45**	89%	60:40
8	Cat***I-46**	No reaction	-
9	Cat***I-30**	87%	52:48
10	Cat***I-47**	92%	60:40
11	Cat***I-18**	90%	60:40
12	Cat***I-48**	81%	62:38
13	Cat***I-49**	86%	67:33
14	Cat***I-50**	88%	55:45
15	Cat***I-51**	90%	57:43
16	Cat***I-38**	84%	53:47
17	Cat***I-52**	94%	51:49
18	Cat***I-53**	94%	**71:29**
19	Cat***I-54**	90%	66:34
20	Cat***I-55**	89%	56:44
21	Cat***I-56**	85%	51:49



After an intensive screening of various reaction parameters with the hope of reaching highly enantioenriched α,α-disubstituted γ-lactone, no better results were obtained. The difficulty of inducing the enantioselectivity could probably be explained by the presence of two H-bond sites on the substrate (N-H of the secondary amide, and the α-acidic proton) and two strong coordinating functional groups (nitro and amide) which complicate the electronic interaction with the *Cinchona* alkaloid for a good transition state. To answer this problematic, one of the solution could have been to try other family of organocatalysts such as Jacobsen's thiourea derivatives[108] or phosphoric acid derivatives.

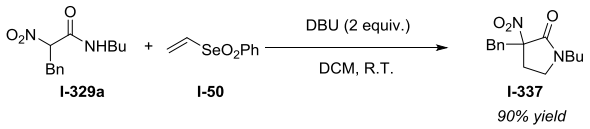
Nonetheless, we decided to put this enantioselective Michael addition/S_N2 sequence in stand-by. The optimum conditions found consisted of performing the reaction of **I-329b** and **I-50** in the presence of **Cat*I-53** in toluene at -20 °C.Under these conditions lactone **I-336** was isolated, after acidic treatment, in 94% yield with an *er* of 71:29.



Scheme 91: Best result for the *Cinchona alkaloid*-catalyzed enantioselective conjugated addition.

Other interesting product isolated during the study

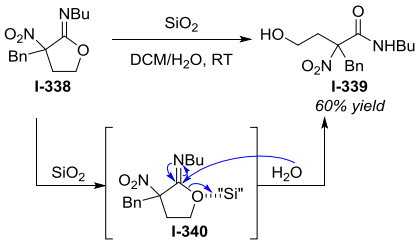
During this project, some interesting building blocks have been isolated. By varying the Brønsted base, we observed that *N*-substituted α-substituted α-nitroacetamide could be exclusively converted to lactam **I-337**. By adding 2 equivalents of DBU in the presence of α-nitroacetamide **I-329a** and phenyl vinyl selenone **I-50** in DCM, the racemic lactam **I-337** was obtained with the excellent yield of 90% (Scheme 92). This result was in accord with the work described by Marini and coworkers.[106]



Scheme 92: α,α-Disubstituted lactam synthesis.

Interestingly, we also noticed that the imidate **I-338** can be hydrolyzed to 2-benzyl-*N*-butyl-4-hydroxy-2-nitrobutanamide **I-339** in the presence of wet DCM and SiO_2. The linear product was formed in 60% yield (Scheme 93).

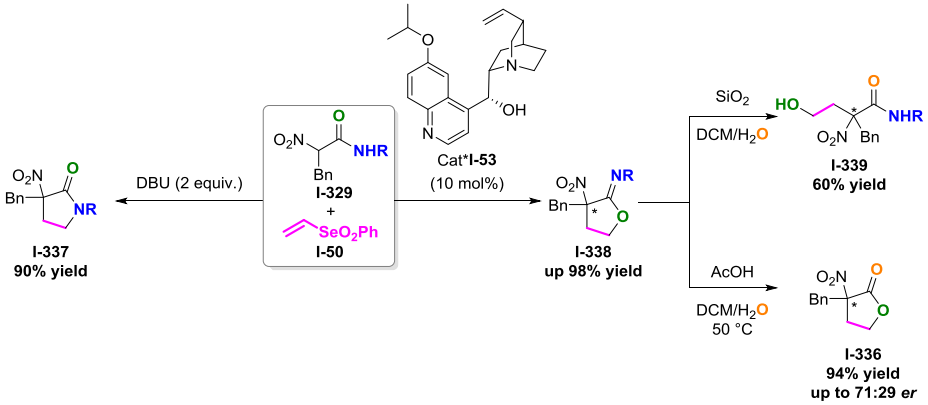
[108] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901.



Scheme 93: Unexpected ring opening of the cyclic imidate I-338.

Conclusion

In conclusion, the organocatalytic Michael addition/intramolecular S_N2 sequence between *N*-substituted α–substituted α–nitroacetamide **I-329** and phenyl vinyl selenone **I-50** has been developed. In the presence of *Cinchona* alkaloid **Cat*I-53**, the formation of cyclic imidate **I-338** was possible and could be converted after hydrolysis to the α,α-disubstituted γ-lactone **I-336** in excellent yield and moderate enantioselectivity. This domino process could afford the linear product **I-339** if the imidate **I-338** was treated with SiO_2 and wet DCM. The racemic synthesis of α,α-disubstituted γ-lactam **I-337** was also feasible in excellent yield using DBU. In this methodology, the careful choice of the reaction conditions allowed the formation of different important building blocks which could be used later for the design of potent bioactive molecules (Scheme 94).



Scheme 94: α–Alkyl α–nitroacetamide and phenyl vinyl selenone for the synthesis of γ-lactone or γ-lactam.

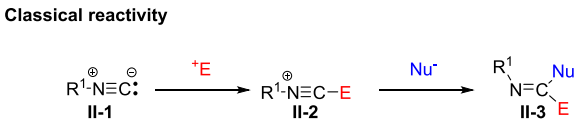
<u>Part II:</u> Transition Metal-Catalyzed Insertions of Isocyanides Bearing Participating Functional Group

Chapter 3: Lewis Acid-Catalyzed Insertions of α,α-Disubstituted α-Isocyanoacetate and Methyl *o*-Isocyanobenzoate

Introduction

Isocyanide as nucleophile

The unique electronic configuration of isocyanide affords to this functional group a peculiar reactivity. [109] Classically, due to the free lone pair located on the carbon, isocyanide **II-1** acts as a nucleophile with electrophiles. The resultant nitrilium **II-2** reacts quickly with an external nucleophile which leading to the ketimine **II-3** (Scheme 95).

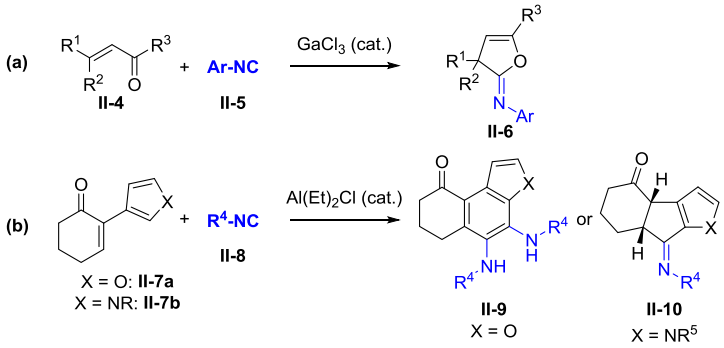


Scheme 95: Classical reactivity of isocyanide.

The use of Lewis acids has been described for years to enhance the electrophilicity of functionalities such as carbonyl, imine, carboxylate or nitrile groups and numerous transformations like Diels-Alder,[110] or Friedel-Craft[111] reactions have been developed using Lewis acid catalysis.

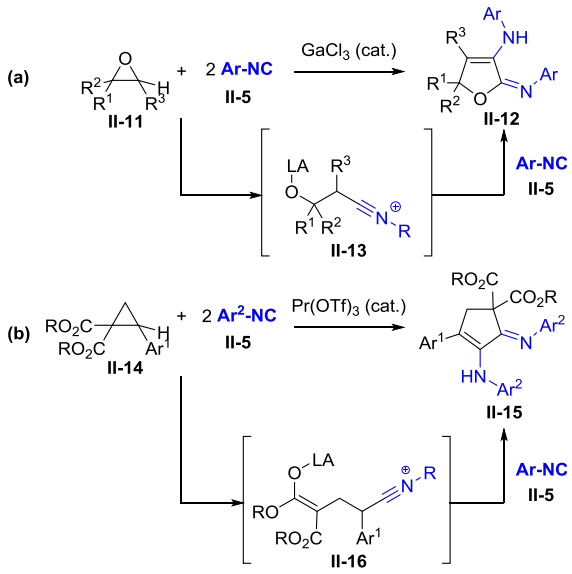
To introduce nucleophilic isocyanides in unreactive substrate, different functionalities have been activated by Lewis acid. In the beginning of this century, Chatani and coworkers have reported the $Ga(Cl)_3$-catalyzed [4+1] cycloaddition of α,β-unsaturated ketones **II-4** with aryl isocyanides **II-5** (Scheme 96, **(a)**). This reaction offered various cyclic imidates **II-6** which could be converted in γ-lactones.[112a] Other Michael acceptors such as 2-aryl 2-cyclohexen-1-ones **II-7** lead to [4+1] cycloaddition with isocyanide when $La(OTf)_3$ was used as catalyst (Scheme 96, **(b)**). Two different products (**II-9** or **II-10**) could be isolated depending on the internal heterocycle attached to the cyclic enone.[112b]

[109] (a) A. V. Lygin, A. de Meijere, *Angew. Chem. Int. Ed*. **2010**, *49*, 9094; (b) M. Tobisu, N. Chatani, *Chem. Lett.* **2011**, *40*, 330; (c) G. Qiu, Q. Ding, J. Wu, *Chem. Soc. Rev*. **2013**, *42*, 5257; (d) S. Lang, *Chem. Soc. Rev*. **2013**, *42*, 4867; (e) T. Vlaar, E. Ruijter, B. U. W. Maes, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2013**, *52*, 7084; (f) S. Chakrabarty, S. Choudhary, A. Doshi, F.-Q. Liu, R. Mohan, M. P. Ravindra, D. Shah, X. Yang, F. F. Fleming, *Adv. Synth. Catal*. **2014**, *356*, 2135; g) B. Song, B. Xu, *Chem. Soc. Rev*. **2017**, *46*, 1103; h) M. Giustiniano, A. Basso, V. Mercalli, A. Massarotti, E. Novellino, G. C. Tron, J. Zhu, *Chem. Soc. Rev*. **2017**, *46*, 1295.
[110] F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro, *Eur. J. Org. Chem.* **2001**,439.
[111] S.-L., You, Q. Cai, M. Zeng, *Chem. Soc. Rev*. **2009**, *38*, 2190.
[112] (a) N. Chatani, M. Oshita, M. Tobisu, Y. Ishii, S. Murai, *J. Am. Chem. Soc.* **2003**, *125*, 7812; M. Oshita, K. Yamashita, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2005**, *127*, 761; (b) J. D. Winkler, S. M. Asselin, *Org. Lett.* **2006**, *8*, 3975.



Scheme 96: Lewis acid-catalyzed transformation of α,β-unsaturated enone and isocyanide.

Zhao and coworkers have shown that gallium-(III) could also catalyze the double insertion of isocyanide **II-5** into substituted epoxide **II-11** for the synthesis of α,β-unsaturated α-iminolactones **II-12**.[113] In this transformation, the Lewis acid activated the epoxide which facilitated the ring opening by nucleophilic addition of an isocyanide. The subsequent nitrilium **II-13** reacted with a second isocyanide to afford, after closing the 5-membered ring, the desired cyclic compound **II-12** in good yield (Scheme 97, **(a)**). Similarly, Meijere *et al* have reported the $Pr(OTf)_3$-catalyzed double insertion of isocyanide **II-5** into electron deficient cyclopropane **II-14** to afford the cyclic enamine **II-15** in low to moderate yield (Scheme 97, **(b)**).[114]

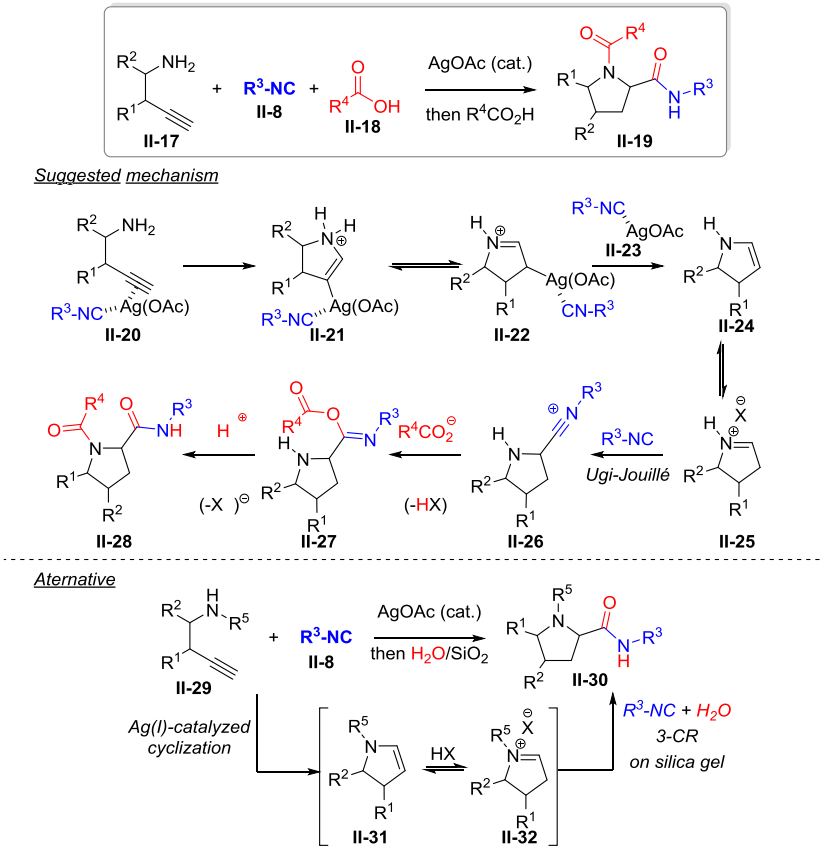


Scheme 97: Lewis acid-catalyzed double isocyanide insertion into epoxide or activated cyclopropane.

[113] G. Bez, C.-G. Zhao, *Org. Lett.* **2003**, *5*, 4991.
[114] V. S. Korotkov, O. V. Larionov, A. de Meijere, *Synthesis* **2006**, 3542.

Recently, our group reported the silver-(I)-catalyzed 3-CR reaction of primary homopropargylamine **II-17**, isocyanide **II-8** and carboxylic acid **II-18** for the synthesis of *N*-acyl proline α-amides **II-19** (Scheme 98, **(a)**).[115] For this reaction, the suggested mechanism which followed our experimental observations started with a silver-catalyzed 5-*endo*-dig cyclization of the amine **II-20** to the internal alkyne. After expulsion of the silver complex linked on **II-22**, **II-22** was converted to the dihydropyrrole **II-24**. With the presence of the isocyanide **II-8** and the carboxylic acid **II-18**, this cyclic compound **II-24** which was in equilibrium with the iminium intermediate **II-25** underwent an Ugi-Jouillé reaction to afford the desired pyrrolidine derivative **II-28**.

It was important to note that in the absence of carboxylic acid **II-18** and if the primary homopropargylamine **II-17** was replaced by the secondary amine **II-29**, the transformation stoped at the protected dihydropyrrole **II-31**. The 3-CR reaction between the intermediate **II-32**, water and isocyanide occurred only if the reaction mixture was submitted to FCC on silica gel and lead to the *N*-protected proline α-amides **II-30** (Scheme 98, **(b)**).

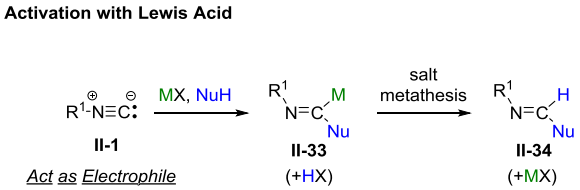


Scheme 98: Silver-catalyzed 3-CR with isocyanide.

[115] S. Tong, C. Piemontesi, Q. Wang, M.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 7958.

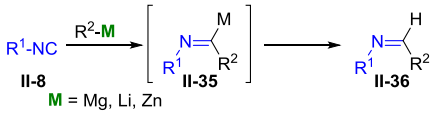
Isocyanide as electrophile

By taking advantage of the carbene-like nature of isonitrile **II-1**, this functional group could also react as an electrophile when a specific metal was present in the reaction (Scheme 99). Ito and Saegusa, the pioneers in this type of isocyanide insertion to nucleophiles, have developed this chemistry at the end of the sixties. Amine,[116] trialkylsilane,[117] alcohol,[118] thiol[119] and dialkylphosphine[120] have been used in copper-(I) or copper-(II)-catalyzed isocyanide insertion reaction.



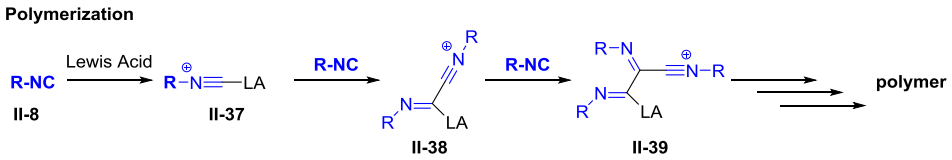
Scheme 99: Electrophilic isocyanide: activation with Lewis acid.

Later, it has been highlighted that the isocyanide insertion into nucleophile was also possible without external activation if strong metalated nucleophiles such as Grignard reagent, organolithium or organozinc compounds were used (Scheme 100).[121]



Scheme 100: Organometallic as strong nucleophile.

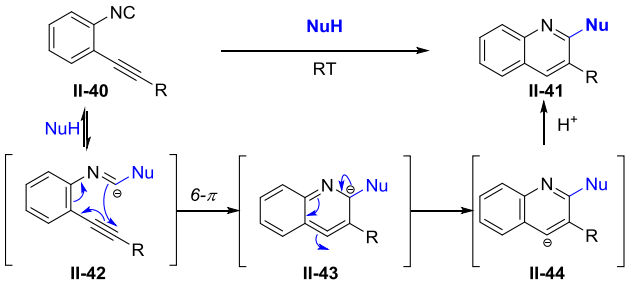
In the field of polymer chemistry, Lewis acids have been utilized to promote the isocyanide polymerization (Scheme 101).[122] With this type of activation and by playing with the temperature and the alkyl/aryl residue of the isocyanide, different oligomers with various physical and chemical properties have been elaborated.



Scheme 101: Polymerization of isocyanide.

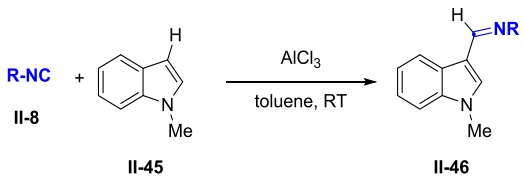
[116] T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, H. Yoshioka, *Tetrahedron Lett.* **1966**, *7*, 6121.
[117] T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, *J. Am. Chem. Soc.* **1967**, *89*, 2240.
[118] T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, *Tetrahedron Lett.* **1967**, *8*, 521.
[119] T. Saegusa, S. Kobayashi, K, Hirota, Y. Okumura, Y. Ito, *Bull. Chem. Soc. Jap.* **1968**, *41*, 1638.
[120] T. Saegusa, Y. Ito, S. Kobayashi, *Tetrahedron Lett.* **1968**, *9*, 935.
[121] Lithium magnesium: (a) G. E. Niznic, W. H. Morrison, H. M. Walborsky, *J. Org. Chem.***1974**, *39*, 600. (b) zinc: M. Murakami, H. Ito, Y. Ito, *J. Org. Chem.* **1988**, *53*, 4158.
[122] F. Millich, *Chem. Rev.* **1972**, *72*, 101.

In 1999, Ito and coworkers reported the isocyanide insertion into organic nucleophile such as dialkyl amine and alcohol without external activation (Scheme 102).[123] In this particular case, the nucleophile reacted with the *o*-alkynylisocyanobenzenes **II-40** to afford the imdoyl anion **II-42** which directly underwent a fast 6π–electrocyclization. After rearomatization and protonation, the quinoleine **II-41** was formed in good yield. Normally, the nucleophilic addition on isocyanide was delicate without catalyst but the favored 6π–electrocyclization allowed the trapping of the intermediate **II-42** to drive the reaction to the final product **II-41**.



Scheme 102: Isocyanide insertion of nucleophiles followed by 6-π electrocyclization

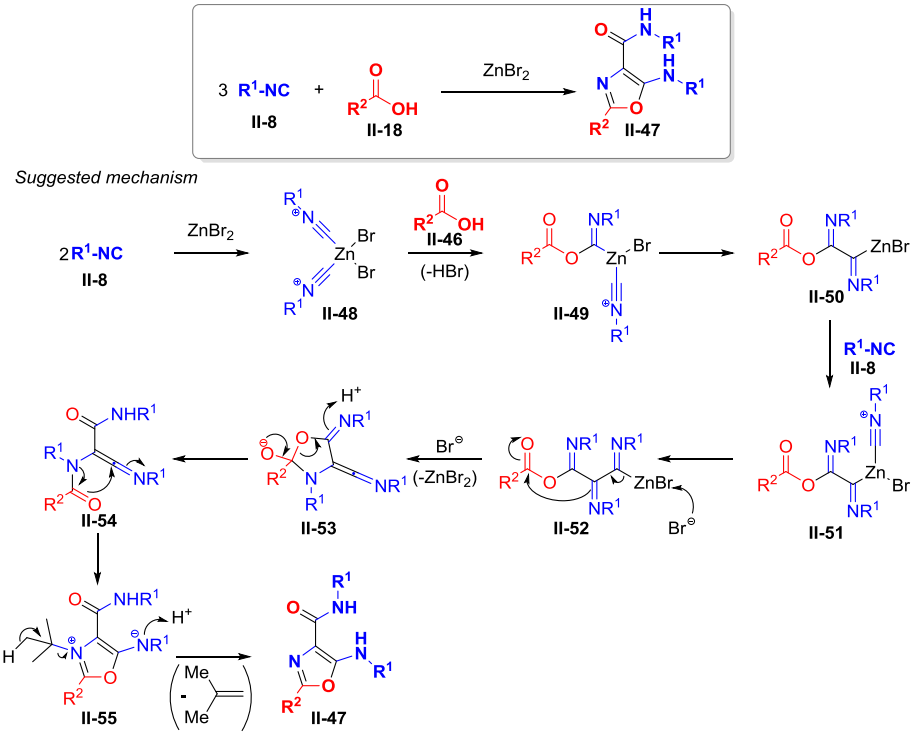
The isocyanide insertion of indole **II-45** was also possible and has been described by Chatani and coworkers in 2007 if aluminum trichloride was used as Lewis acid (Scheme 103).[124]



Scheme 103: Isocyanide insertion of indole.

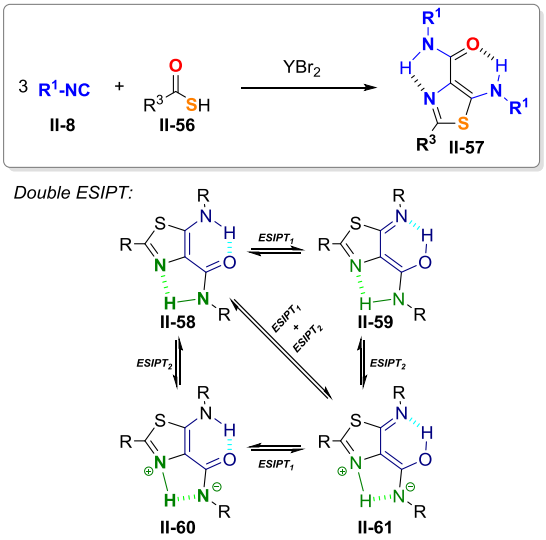
More recently, our group described the 4-CR reaction where three molecules of isocyanide **II-8** reacted with carboxylic acid **II-18** in the presence of zinc bromide as Lewis acid (Scheme 104, **(a)**).[125] Mechanistically, this transformation could start with isocyanides **II-8** coordinated to the Lewis acid. After isocyanide insertion of carboxylic acid **II-18** to give **II-48**, two other isocyanide insertions occured to afford the oligomer **II-52** containing three isocyanides unit. Then, metal-salt elimination lead to the ketenimine intermediate **II-54** which delivered after cyclization and dealkylation the heterocycle **II-47** in moderate to good yields.

[123] M. Suginome, T. Fukuda, Y. Ito, *Org. Lett.* **1999**, *1*, 1977.
[124] M. Tobisu, S. Yamaguchi, N. Chatani, *Org. Lett.* **2007**, *9*, 3351.
[125] Y. Odabachian, S. Tong, Q. Wang, M.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2013**, *52*, 10878.



Scheme 104: Lewis acid-catalyzed reaction of isocyanides with carboxylic acid

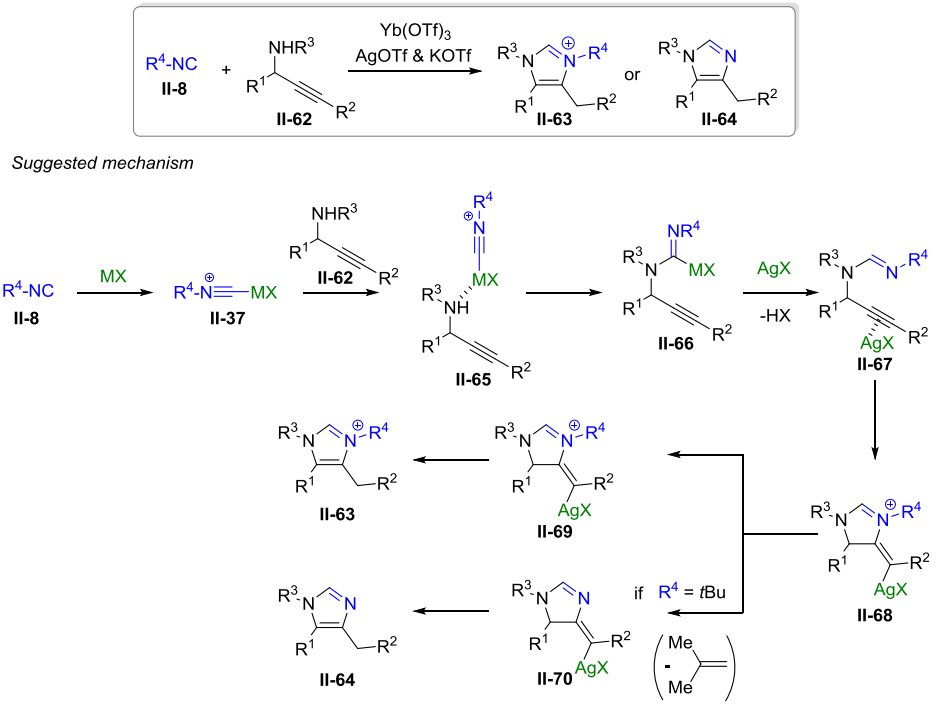
Thiocarboxylic acid **II-56** could replace carboxylic acid **II-18** and allowed the similar formation of amino-4-carboxamidothiazole **II-57** (Scheme 105).[126] Interestingly, this type of heterocycles was able to emit fluorescence at long wavelengths due to the double excited-state intramolecular proton transfer (ESIPT) process.



Scheme 105: Lewis acid-catalyzed reaction of isocyanides with thiocarboxylic acid and double ESIPT process.

[126] S. Tong, S. Zhao, Q. He, Q. Wang, M.-X. Wang, J. Zhu *Angew.Chem. Int. Ed.* **2017**, *56*, 6599.

The syntheses of imidazolium salts **II-63** and imidazoles **II-64** by using Lewis acids, isocyanide **II-8** and propargylamine **II-62** have also been developed in our laboratory (Scheme 106).[127] In this reaction, the isocyanide **II-8** acted as a polarized triple bond which was uncommon and rare for this type of functionality. For the mechanism, we suggested that the propargylamine **II-62** would attack the Lewis acid-activated isocyanide **II-37** to afford the metalated species **II-66**. After salt metathesis, the compound **II-67**, where the triple bond was activated by the silver salt, would afford the cyclic compound **II-68** after 5-*exo*-dig type reaction. Silver salt regeneration permited the formation of the desired imidazolium salt **II-63**. If the residue carried by the nitrogen was a *tert*-butyl group, a dealkylation was occurring to give the imidazolone **II-64** after salt metathesis.



Scheme 106: Lewis acids-catalyzed reaction of isocyanide and propargylamine.

Isocyanide synthesis

To synthesize isocyanides, several methods have been developed over the years. Preliminary studies from Lieke and later Meyer and Gauthier separately described the formation of isonitrile **II-8** by reacting alkyl halide **II-71** with silver cyanide (Scheme 107 **(a)**).[128] Primary amines **II-72** were a partner of choice for the preparation of isocyanide **II-8**. Excess of KOH and $CHCl_3$ in the presence of the primary amine **II-72** afforded the isonitrile compound **II-8** (Scheme 107 **(b)**).[129] However, the most common method used to construct isocyanide **II-8** was the two steps sequence formylation/dehydration of primary amine **II-72**.

[127] S. Tong, Q. Wang, M.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 1293.
[128] E. Meyer, *J. Prakt. Chem.* **1866**, 147 (b) A. Gautier, *Justus Liebigs Ann. Chem.* **1867**, *142*, 289.
[129] A. W. Hofmann, *Justus Liebigs Ann. Chem.* **1867**, *144*, 114.

With different formylating agent (ethylformate, acetic formic anhydride, ammonium formiate or even trifluoromethanesulfonic anhydride to activate the amine) and numerous conditions of dehydration (with $POCl_3$, $COCl_2$, PPh_3 & CCl_4, Burgess reagent etc.) a broad scope of isocyanides **II-8** has been reported.[130]

Alcohol **II-74**, a versatile starting material, is also convertible in isocyanide **II-8**. Hard Lewis acids, such as $ZnBr_2$ or $TiCl_4$, in present of TMSCN could be used to transform tertiary protected and non-protected alcohol. Recently, Shenvi and co-worker have reported milder condition where the reaction of TFA-protected alcohol **II-73** with 20 mol% of $Sc(OTf)_2$ and TMSCN at room temperature lead to the isocyanation with high stereo-inversion (Scheme 107, **(c)**).[131] With this method, the late installation of isocyanide in elaborated molecules was possible with good chemo- and stereoselectivities. Other methods to convert free alcohol **II-74** to isocyanide **II-8** have also been described by the group of Kitano and Mukayaima respectively (Scheme 107, **(d)**).[132] Gassman *et al* have shown that the opening of cyclic ethers **II-75** using ZnI_2 and TMSCN permited the preparation of β– or γ–isocyanoalcohol **II-76** (Scheme 107, **(e)**).[133] Finally, isocyanate **II-77** could be modified to isocyanide **II-8** under reductive condition (Scheme 107, **(f)**).[134]

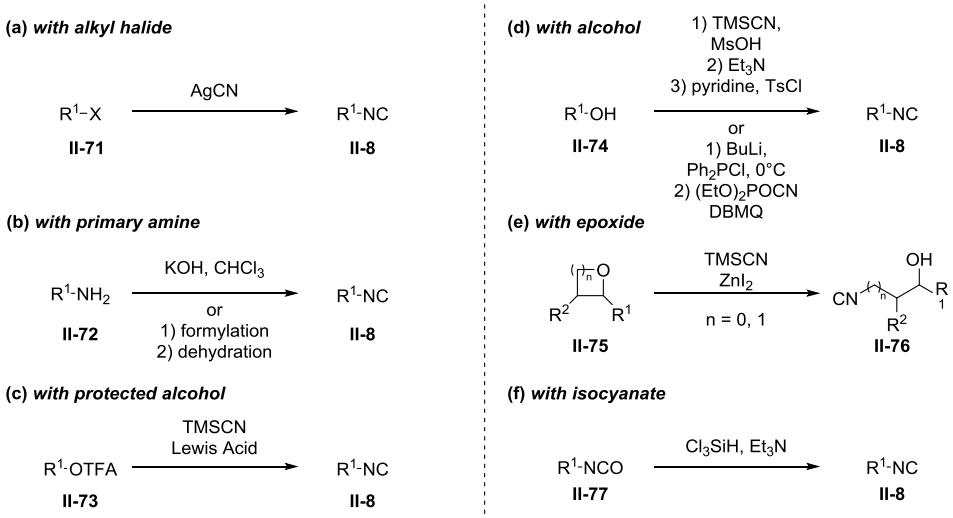
[130] (a) $(CF_3SO_2)O$ as formylating agent: I. A. O'Neil, J. Baldwin, *Synlett* **1990**, 603; (b) With $COCl_2$ and $POCl_3$: I. Ugi, R. Meyr, *Angew. Chem.* **1958**, *70*, 702; I. Ugi, R. Meyr, *Chem. Ber.* **1960**, *93*, 239; (c) with PPh_3, CCl_4: R. Appel, R. Kleistück, K. D. Ziehn *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 132; (d) with Burgess reagent: S. M. Creedon, H. K. Crowley and D. G. McCarthy, *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 1015.; K. W. Quasdorf, A. D. Huters, M. W. Lodewyk, D. J. Tantillo, N. K. Garg, *J. Am. Chem. Soc.* **2012**, *134*, 1396-1399; (e) For other dehydrating agent see: M. L. Bode, D. Gravestock, A. L. Rousseau *Org. Prep Proc. Int* **2016**, *48*, 89.

[131] (a) With $TiCl_4$: E. J. Corey, P. A. Magriotis, *J. Am. Chem. Soc.* **1987**, *109*, 289; (b) with $Sc(OTf)_2$: S. V. Pronin, R. A. Shenvi, *J. Am. Chem. Soc.* **2012**, *134*, 19604.

[132] I. Okada, Y. Kitano, *Synthesis* **2011**, No. 24, 3997; K. Masutani, T. Minowa, Y. Hagiwara, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1106.

[133] P. G. Gassman, T. L. Guggenheim, *J. Am. Chem. Soc.* **1982**, *104*, 5849; P. G. Gassman, *Tetrahedron Lett.* **1985**, *26*, 4971.

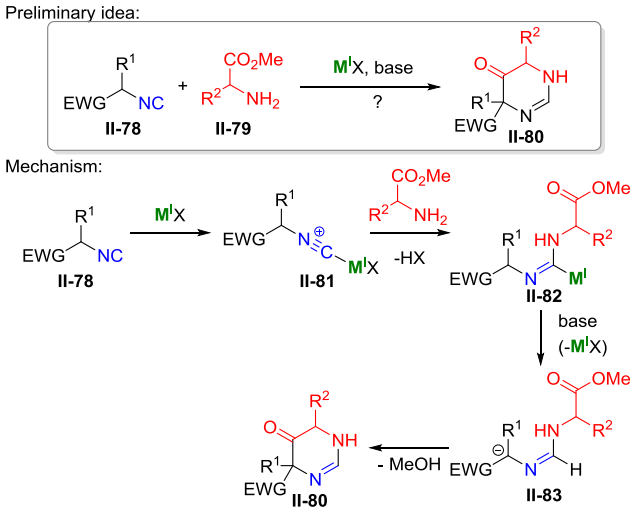
[134] *A. W. Hofmann, Ber. Dtsch. Chem. Ges.* **1870**, *3*, 766.; J. E. Baldwin, J. C. Bottaro, P. D. Riordan, A. E. Derome, *J. Chem. Soc., Chem. Commun.*, **1982**, 942.



Scheme 107: Different approaches for the synthesis of isocyanide.

Preliminary idea

With the isocyanide insertion into nucleophile in mind, we envisaged to develop the Lewis acid-catalyzed [3+3] cycloaddition of α-EWG isocyanide **II-78** and α-amino acetate **II-79** for the synthesis of 1,6-dihydropyrimidin-5(4*H*)-one derivative **II-80** (Scheme 108). In this transformation, we imagined that the mechanism could start with the isocyanide coordination of the Lewis acid which promoted the nucleophilic attack of the α-amino acetate **II-79** to offer the amidine **II-82**. Sequential salt metathesis and deprotonation gave the intermediate **II-83** which underwent cyclization to deliver the desired 6-membered ring **II-80**. This unprecedented domino process involving isocyanide insertion/cyclization could allow the formation of one C-N and one C-C bonds rapidly to furnish unusual building blocks.

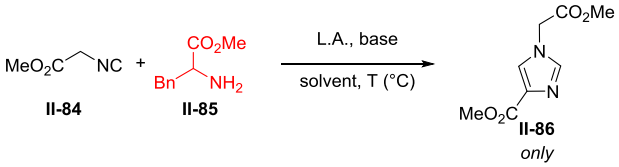


Scheme 108: Preliminary idea - Lewis acid-catalyzed [3+3] cycloaddition.

Results & Discussion

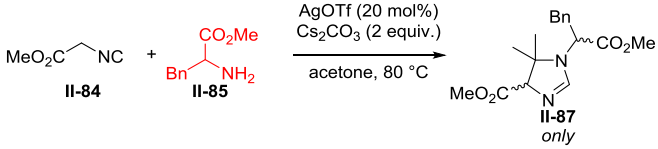
Preliminary resutls

To start our investigation on the Lewis acid-catalyzed formal [3+3] cycloaddition we decided to use methyl α-isocyanoacetate **II-84** and *L*-phenylalanine methyl ester **II-85** as partners. Different parameters (Lewis acid, base, solvent, temperature) were intensively screened but, unfortunately, only the dimer **II-86** was observed which comes from the [3+2] cycloaddition of two isocyanoacetate molecules **II-84**. This was not surprising, Yamamoto and coworkers have already described this type of transformation where one of the isocyanide was playing the role of a 1,3-dipole due to the presence of a base or a Lewis acid (Scheme 109).[135]



Scheme 109: [3+2] Cycloaddition of α-isocyanoacetates.

During this preliminary exploration, we have also isolated the 2-imidazoline derivative **II-87** when acetone was used as solvent. This compound **II-87** results from the 3-CR reaction of α-isocyanoacetate **II-84**, α-aminoester **II-85** and acetone. This multicomponent reaction was known and has been depicted by Orru, Ruijter and coworkers in 2007. [136]



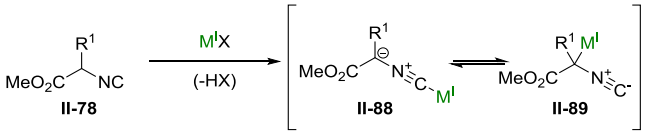
Scheme 110: 3-CR reaction for the synthesis of imidazolines derivatives.

Methyl α-phenyl α-isocyanoacetate has been used as α-isocyanoacetate alternative with the hope of developing this Lewis acid-catalyzed [3+3] cycloaddition. This time, only degradation of the starting materials was observed whatever the Lewis acid, base, temperature or solvent used. These observations drove us to conclude that the presence of an acidic α-proton was problematic in the design of our reaction.

[135] C. Kanazawa, S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 10662.
[136] N. Elders, R. F. Schmitz, F. J. J. De Kanter, E. Ruijter, M. B. Groen, R. V. A. Orru, *J. Org. Chem.* **2007**, *72*, 6135.

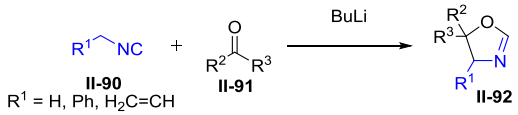
α-Metalated isocyanide

With the well-known electron withdrawing ability of the isocyanide functionality, the deprotonation of the α-proton was possible with a strong base (BuLi) or even with a softer base when another EWG is carried by the α-carbon. This was the case for the isocyanoacetate **II-78** and lot of methodologies have been developed by taking advantage of this property.[137,109a] It was also possible to incorporate a Lewis acid in the reaction condition to activate the isocyanide which enhanced the acidity of the α-CH and facilitated the deprotonation to form the intermediate **II-88**. A 1,3-metal shift could occurred on **II-88** to afford the α-metalated species **II-89** (Scheme 111). This two forms were in equilibrium and could be considered as a reactive 1,3-dipole used in different cycloadditions.



Scheme 111: α-Metalated isocyanoacetate, formation of a 1,3 dipole.

The first example of α-metalated isocyanide in organic synthesis has been reported by Schöllkopf and Gerhart in 1968 for the synthesis of oxazoline **II-92** (Scheme 112).[138] In this reaction butyl lithium was mandatory to deprotonate alkyl isocyanide **II-90**.

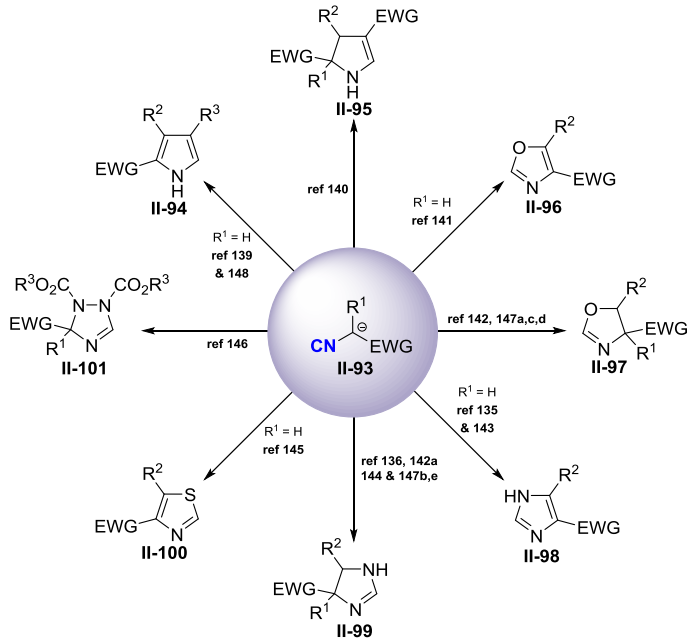


Scheme 112: First [3+2] cycloaddition using α-metalated isocyanide.

Over the years various syntheses of 5 membered heterocycles have been elaborated by taking advantage of the α-metalated α-EWG isocyanide (Scheme 113). Pyrroles **II-94** (with Michael acceptor or alkyne)[139], pyrrolines **II-95** (with Michael acceptors),[140] oxazoles **II-96** (with aldehyde),[141] oxazolines **II-97** (with aldehyde or ketone),[142] imidazoles **II-98** (with

[137] (a) A. V. Guelvich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev.* **2010**, *110*, 5235; (b) V. P. Boyarskiy, N. A. Bokach, K. V. Luzyanin, V. Y. Kukushkin, *Chem. Rev.* **2015**, *115*, 2698.
[138] U Schöllkopf, F. Gerhart, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 805.
[139] Pyrrole: (a) D. H. R. Barton, S. Z. Zard, *J. Chem. Soc. Chem. Commun.* **1985**, 1098; (b) O. V. Larionov, A. de Meijere, *Angew. Chem., Int. Ed.* **2005**, *44*, 5664; (c) S. Kamijo, C. Kanazawa, Y. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 9260. (d) A. V. Lygin, O. V. Larionov, V. S. Korotkov, A. de Meijere, *Chem. - Eur. J.* **2009**, *15*, 227.
[140] Pyrroline: (a) R. Grigg, M. I. Lansdell, M. Thornton-Pett, *Tetrahedron* **1999**, *55*, 2025; (b) C. Guo, M.-X. Xue, M.-K. Zhu, L.-Z. Gong, *Angew. Chem., Int. Ed.* **2008**, *47*, 3414; (c) J. Song, C. Guo, P.-H. Chen, J. Yu, S.-W. Luo, L.-Z. Gong, *Chem. – Eur. J.* **2011**, *17*, 7786; (d) M.-X. Zhao, D.-K. Wei, F.-H. Ji, X.-L. Zhao, M. Shi, *Chem. – Asian J.*, **2012**, *7*, 2777.
[141] Oxazole: (a) P.-L. Shao, J.-Y. Liao, Y. A. Ho, Y. Zhao, *Angew. Chem., Int. Ed.* **2014**, *53*, 5435; (b) R. Mossetti, T. Pirali, G. C. Tron, J. Zhu, *Org. Lett.* **2010**, *12*, 820. (c) M. Baumann, I. R. Baxendale, S. V. Ley, C. D. Smith, G. K. Tranmer, *Org. Lett.* **2006**, *8*, 5231; (d) Q. Wang, Q. Xia, B. Ganem, *Tetrahedron Lett.* **2003**, *44*, 6825; (e) J. Tang, J. G. Verkade, *J. Org. Chem.* **1994**, *59*, 7793.

isocyanide, aldimine),[135,143] imidazoline **II-99** (with aldimine or ketimine), [141a,144] thiazole **II-100** (with thiono ester or carbone disulphide)[145] and triazolines **II-101** (with azodicarboxylates)[146] could be made with this approach.

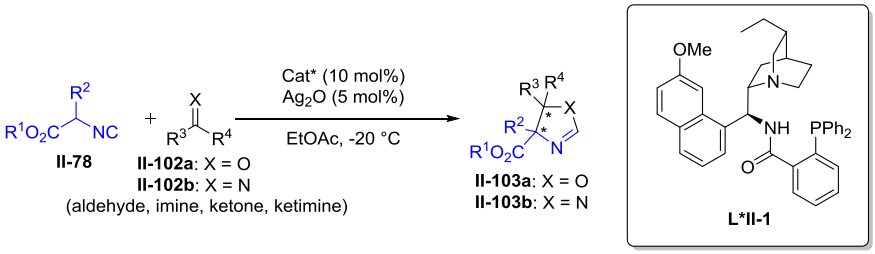


Scheme 113: [3+2] Cycloaddition for heterocycles syntheses using α-methalated isocyanide.

Several asymmetric methodologies have been developed with the α-metalated isocyanoacetate **II-73** to synthesize enantioenriched non-aromatic 5 membered heterocycles. For example, Dixon and coworkers have highlighted the highly enantio- and diastereoselective synthesis of oxazolines **II-103a** using silver salt as Lewis acid and a phosphinated *cinchona* alkaloid derivative **L*II-2** as precatalyst (Scheme 114). In this asymmetric aldol reaction where the isocyanoacetate **II-78** acted as a nucleophile on a carbonyl compound **II-102a**, the cooperative Brønsted base/Lewis acid catalyst system was the key to get the hetereocycles in excellent yields and *ee*. By changing the carbonyl

[142] Oxazoline: M.-X. Zhao, H. Zhou, W.-H. Tang, W.-S. Qu, M. Shi, *Adv. Synth. Catal.* **2013**, *355*, 1277; (b) H. Y. Kim, K. Oh, *Org. Lett.* **2011**, *13*, 1306; (c) M.-X. Xue, C. Guo, L.-Z. Gong, *Synlett* **2009**, 2191; (c) D. Benito-Garagorri, V. Bocokiæ, K. Kirchner, *Tetrahedron Lett.* **2006**, *47*, 8641. (d) V. A. Soloshonok, A. D. Kacharov, D. V. Avilov, K. Ishikawa, N. Nagashima, T. Hayashi, *J. Org. Chem.* **1997**, *62*, 3470.
[143] Imidazolone (a) G. S. M. Sundaram, B. Singh, C. Venkatesh, H. Ila, H. Junjappa, *J. Org. Chem.* **2007**, *72*, 5020; (b) S. Kamijo, Y. Yamamoto, *Chem. - Asian J.* **2007**, *2*, 568; (d) M.-X. Zhao, H.-L. Bi, R.-H. Jiang, X.-W. Xu, M. Shi, *Org. Lett.* **2014**, *16*, 4566.
[144] Imidazoline: (a) J. Aydin, K. S. Kumar, L. Eriksson, K. H. Szabó, *Adv. Synth. Catal.* **2007**, *349*, 2585; (b) Y. Lin, X. Zhou, L. Dai, J. Sun, *J. Org. Chem.* **1997**, *62*, 1799.
[145] Thiazole: (a) U. Schöllkopf, P. Porsch, E. Blume, *Liebigs Ann. Chem.* **1976**, *11*, 2122. (b) G. Hartman, L. Weinstock, *Synthesis* **1976**, 681.
[146] Triazole: D. Monge, K. L. Jensen, I. Marin, K. A. Jørgensen, *Org. Lett.* **2011**, *13*, 328.

compound **II-102a** to an imine derivative **II-102b**, highly enantio- and diastereoselective Mannich reactions were also possible and furnished enantioenriched imidazolines **II-103b**.[147]



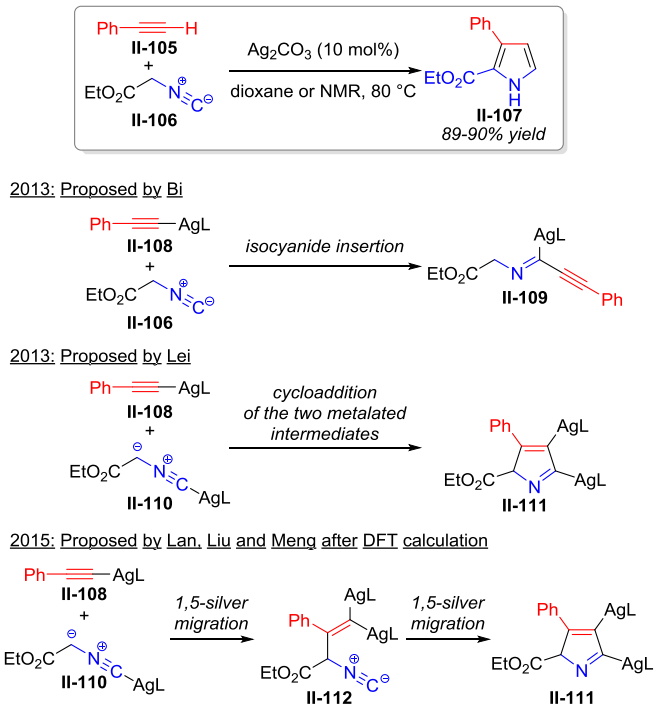
Scheme 114: Enantioselective and diastereoselective [3+2] cycloaddition of isocyanoacetate and carbonyl compounds.

Some obscurities on the mechanism of the Lewis acid-catalyzed [3+2] cycloaddtion using isocyanoacetate were still remaining and intriguingly, the groups of Bi and Lei reported separately the same year two different mechanistic approaches for the same silver carbonate-catalyzed [3+2] cycloaddition of phenylacetylene **II-105** and isocyanoacetate **II-106** (Scheme 115). In the Bi's suggested mechanism, the first step was the isocyanide insertion into metalated alkyne **II-108** whereas in the proposed mechanism of Lei, the 1,3-dipole **II-110** reacted with the silver-alkyne **II-108** *via* a concerted [3+2] cycloaddition.

Two years later, Lan, Liu and Meng observed after DFT calculation that the most favorable pathway should give the dimetalated heterocycle **II-111** proposed by Lei after a double 1,5-silver migration. This computational study discriminated the proposal of Bi and justified the high nucleophilicity of the α-carbon of the isocyanoacetate.[148]

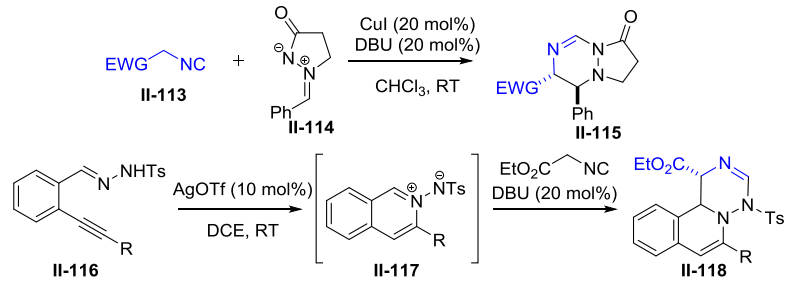
[147] (a) F. Sladojevich, A. Trabocchi, A. Guarna, D. J. Dixon, *J. Am Chem. Soc*. **2011**, *133*, 1710; (b) I. Ortin, D. J. Dixon, *Angew. Chem. Int. Ed.* **2014**, *53*, 3462; (c) R. De La Campa, I. Ortin, D. J. Dixon, *Angew. Chem. Int. Ed.* **2015**, *54*, 4895; (d) A. Franchino, P. Jakubec, D. J. Dixon, *Org. Biomol. Chem.* **2016**, *14*, 93; (e) R. de la Campa, A. D. Gammack Yamagata, I. Ortin, A. Franchino, A. L. Thompson, B. Odell, D. J. Dixon, *Chem. Commun.* **2016**, *52*, 10632.

[148] (a) J. Liu, Z. Fang, Q. Zhang, Q. Liu, X. Bi, *Angew. Chem., Int. Ed.* **2013**, *52*, 6953; (b) M. Gao, C. He, H. Chen, R. Bai, B. Cheng, A. Lei, *Angew. Chem., Int. Ed.* **2013**, *52*, 6958; (c) X. Qi, H. Zhang, A. Shao, L. Zhu, T. Xu, M. Gao, C. Liu, Y. Lan, *ACS Catal.* **2015**, *5*, 6640.



Scheme 115: Silver-catalyzed [3+2] cycloaddition of isocyanoacetate and phenylacetylene.

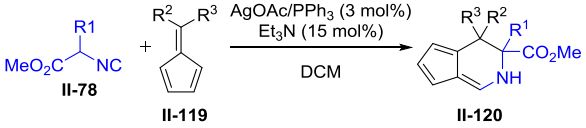
Other partner than 2-atom units have been utilized in the cycloaddition with α-metalated isocyanide. Indeed, it has been shown that the Lewis acid-catalyzed [3+3] cycloaddition of α-acidic isocyanide **II-113** with azomethine imine **II-114** was possible. With this reaction 1,2,4-triazine derivatives **II-115** and **II-118** could be elaborated in moderate to good yield.[149]



Scheme 116: Lewis acid-catalyzed [3+3] cycloaddition of α-acidic isocyanide and azomethine imine.

Fulvenes **II-119** could also be associated with isocyanoacetate **II-78** in a silver-catalyzed [6+3] annulation/isomerization.[150] In this transformation fused dihydropyridine derivatives **II-120** were obtained in good yields and perfect regioselectivities.

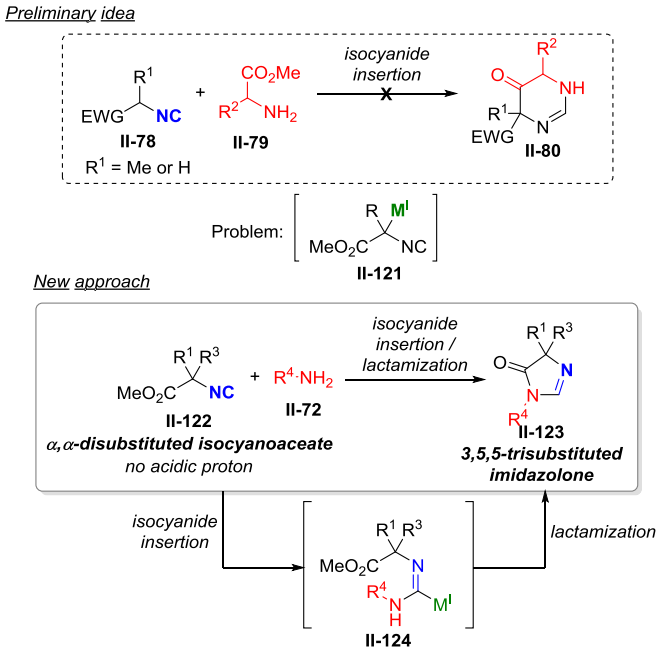
[149] J. Du, X. Xu, Y. Li, L. Pan, Q. Liu, *Org. Lett.* **2014**, *16*, 4004.
[150] Z.-L. He, C.-J. Wang , *Chem. Commun.* **2015**,*51*, 534.



Scheme 117: Silver-catalyzed [6+3] annulation/isomerization of isocyanoacetate and fulvene.

In our preliminary failed experiments, the presence of the α-acidic proton on the α-isocyanoacetate **II-78** facilitated the α-metalation of the isocyanide which rendered the isocyanide insertion into the nucleophile impossible. To overcome this problem, we decided to use α,α-disubstituted isocyanoacetate **II-122** instead of α-mono or non-substituted isocyanoacetate **II-78** and avoided the formation of the 1,3-dipole (Scheme 118).

With this type of isocyanide as starting material, we hoped to develop a novel Lewis acid-catalyzed isocyanide insertion of α,α-disubstituted isocyanoacetate **II-122** into primary amine **II-72**. In this unprecedented domino sequence, lactamization should occur after the isocyanide insertion to afford 3,5,5-trisubstituted imidazolone derivatives **II-123**.

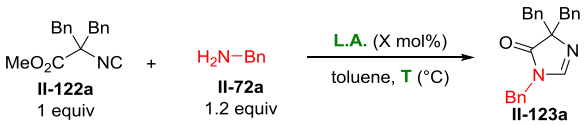


Scheme 118: Alternative to the α-metalated isocyanide.

α,α-Disubstituted isocyanoacetate as partner

With the goal of developing an efficient method to construct imidazolones, we decided to use α,α,-dibenzyl isocyanoacetate **II-122a** and benzyl amine **II-22a** as starting materials and toluene as solvent for the beginning of our investigation. Firstly, different Lewis acids were examined (Table 17). Copper-(II) oxide, ytterbium-(III) triflate or copper-(II) triflate gave no reaction at 60 °C or 80 °C. At 100 °C, no or slow reaction were observed for cupric salts whereas with $Yb(OTf)_3$, decomposition of the starting materials was observed. Impressively, silver-(I) triflate delivered the desired imidazole **II-123a** in 76% isolated yield. In the case of copper-(II) chloride, the formation of imidazole was observable at 80 °C in only 30% NMR yield.

Table 17: Lewis acid screening.

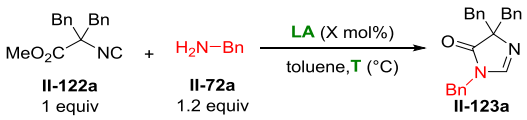


Entry	Lewis Acid	T (°C)	Observation
1	CuO (0.1 equiv.)	60 °C, 80 °C, 100 °C	No reaction
2	CuO (0.2 equiv.)	100 °C	No reaction
3	$Yb(OTf)_3$ (0.1 equiv.)	60 °C, 80 °C	No reaction
4	$Yb(OTf)_3$ (0.1 equiv.)	100 °C	Messy reaction
5	$Cu(OTf)_2$ (0.1 equiv.)	60 °C, 80 °C	No reaction
6	$Cu(OTf)_2$ (0.1 equiv.)	100 °C	Slow conv.
7	Ag(OTf) (0.1 equiv.)	60 °C	Full conv., 76% isolated yield
8	$CuCl_2$ (0.1 equiv.)	60 °C	No reaction
9	$CuCl_2$ (0.1 equiv.)	80 °C	38% conv., 30% NMR yield

With this good result observed with the silver-(I) salt, we decided to continue our screening of different Lewis acids which possessed an oxidation state of +1 (Table 18). At 40 °C, the Cu-(I) salts (Cu_2O and CuCl) did not allow the formation of the heterocycle. However at this same temperature, $AgNO_3$, AgOAc and AgOTf delivered the imidazolone in low to moderate yield. Increasing the temperature to 60 °C gave better outcome and the silver-(I) salts afforded particularly good results. It was not surprising as silver salts have already shown to be powerful catalysts in isocyanide chemistry.[151] After a quick screening of the catalyst loading (Entry 11 to 15), 10 mol% of silver-(I) nitrate gave the best result and offered the imidazole **II-123a** in 90% isolated yield.

[151] Y. Wang, R. K. Kumar, X. Bi, *Tetrahedron Lett.* **2016**, *57*, 5730.

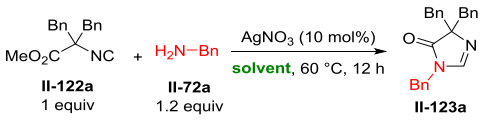
Table 18: Lewis acid screening, second round.



Entry	Lewis acid	Temperature	Yield (%)
1	Cu_2O	40 °C	No reaction
2	CuCl	40 °C	No reaction
3	$AgNO_3$	40 °C	71% conv., 58% NMR yield
4	AgOAc	40 °C	40% conv., 28% NMR yield
5	AgOTf	40 °C	83% conv. 51% NMR yield
6	Cu_2O	60 °C	full conv., 48% NMR yield
7	CuCl	60 °C	full conv., 47% NMR yield
8	$AgNO_3$	60 °C	full conv., quant. NMR yield, (90% isolated)
9	AgOTf	60 °C	full conv., quant. NMR yield, (76% isolated)
10	Ag_2O	60 °C	full conv., quant. NMR yield
11	$AgNO_3$ (5 mol%)	60 °C	full conv.. 83% NMR yield
12	AgOTf (5 mol%)	60 °C	full conv.. 80% NMR yield
13	Ag_2O (5 mol%)	60 °C	75% conv.; 73% NMR yield
14	$AgNO_3$ (1 mol%)	60 °C	80% conv. 67% NMR
15	AgOTf (1 mol%)	60 °C	38% conv. 37% NMR

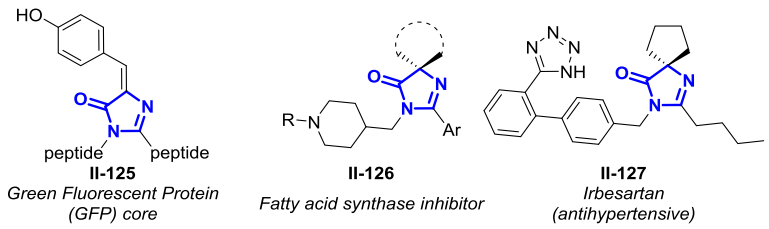
Different solvents were also used in this transformation and AcOEt appeared to give similar results as toluene (Table 19). Increasing the concentration did not impact the reaction and adding molecular sieves was not beneficial for the synthesis of imidazolone **II-123a**.

Table 19: Solvent screening.



Entry	solvent	Observation
1	toluene	Full conv., quant. NMR yield (90% isolated)
2	dioxane	Full conv., 88% NMR yield
3	DCM	74% conv., 69% NMR yield
4	THF	91% conv., 84% NMR yield
5	DMF	78% conv., 75% NMR yield
6	AcOEt	Full conv., quant. NMR yield (90% isolated)
7	toluene + 4 Å MS	83% conv., 81% NMR yield
8	toluene (conc = 0.2 mol.L^{-1})	Full conv., quant. NMR yield (84% isolated)
9	toluene (conc = 0.5 mol.L^{-1})	Full conv., quant. NMR yield

With this mild conditions in hand (toluene, 10 mol% $AgNO_3$, 60 °C), the synthesis of imidazolones **II-123**, important five-membered non-aromatic heterocycles, was possible. These heterocycles are structural motifs found in bioactive natural products[152] and are key elements responsible for the luminescent properties of green fluorescent proteins (GFP) (Scheme 119).[153] Compounds containing this non-aromatic cyclic scaffold display potent inhibitory activities against fatty acid synthases[154] and are angiotensin II receptor antagonists.[155] Indeed, it is the key motif found in the marketed drug Irbesartan **II-127** for the treatment of hypertension.[156]

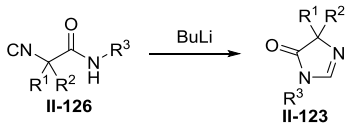


Scheme 119: Important compounds containing imidazolone motif.

[152] (a) D. R. Appleton, M. J. Page, G. Lambert, M. V. Berridge, B. R. Copp, *J. Org. Chem*. **2002**, *67*, 5402; (b) R. A. Edrada, C. C. Stessman, P. Crews, *J. Nat. Prod*. **2003**, *66*, 939.
[153] R. N. Day, M. W. Davidson, *Chem. Soc. Rev.* **2009**, *38*, 2887.
[154] G. C. Bignan, P. J. Connolly, T. L. Lu, M. H. Parker, D. Ludovici, C. Meyer, L. Meerpoel, K. Smans, C. Rocaboy, WO2014039769.
[155] (a) C. A. Bernhart, P. M. Perreaut, B. P. Ferrari, Y. A. Muneaux, J.-L. A. Assens, J. Clement, F. Haudricourt, C. F. Muneaux, J. E. Taillades, M.-A. Vignal, J. Gougat, P. R. Guiraudou, C. A. Lacour, A. Roccon, C. F. Cazaubon, J.-C. Brelihre, G. Le Fur, D. Nisato, *J. Med. Chem.* **1993**, *36*, 3371; (b) I. V. Yampolsky, A. A. Kislukhin, T. T. Amatov, D. Shcherbo, V. K. Potapov, S. Lukyanov, K. A. Lukyanov, *Bioorg. Chem.* **2008**, *36*, 96; (c) L. Wu, K. Burgess, *J. Am. Chem. Soc.* **2008**, *130*, 4089.
[156] https://www.drugbank.ca/drugs/DB01029.

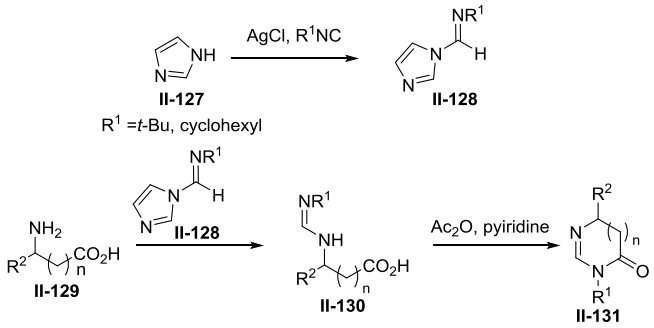
Previous C-2 unsubstituted imidazolone synthesis

Different synthetic routes have been developed for the synthesis of C-2 unsubstituted imidazoles. One of the current methods was the cyclization of α-isocyanoacetamide **II-126** (Scheme 120).[157] By using BuLi, the deprotonation of the N-H occured and promoted the formation of the 5 membered-ring.



Scheme 120: Cyclization of α-isocyanoacetamide for the imidazolone synthesis.

Ito and Saegusa reported the synthesis of imdazolone **II-123** via the cyclization of amino acid derived formamidine **II-130**.[158] In this approach, the reagent **II-128** was synthesized beforehand with imidazole **II-127** and alkyl isocyanide **II-8** in the presence of silver chloride. By mixing aldimine derivative **II-128** with the amino acid **II-129**, the formamidine **II-130** could be isolated. After activation of the carboxylic group with pyridine and acetic anhydride, the C-2 naked 5 or 6-membered heterocycle **II-131** was formed (Scheme 121).



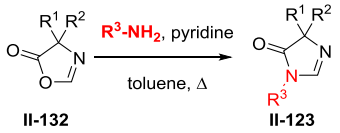
Scheme 121: Cyclization of amino acid derived formamidine for the imidazolone synthesis.

It has also been shown that the conversion of azlactone **II-132** to imidazolone **II-123** was possible. In the presence of an amine in basic condition at reflux, the opening of the azlactone **II-132** was occuring which afforded consequently the imidazolone **II-123**. [159]

[157] (a) K. Matsumoto, M. Suzuki, N. Yoneda, M. Miyoshi, *Synthesis* **1977**, 249. (b) U. Schöllkopf, H.-H. Hausberg, M. Segal, U. Reiter, I. Hoppe, W. Saenger, K. Lindner, *Liebigs Ann. Chem.* **1981**, 439. (c) R. Bossio, S. Marcaccici, P. Paoli, S. Papaleo, R. Pepino, C. Polo, *Liebigs Ann. Chem.* **1991**, 843.

[158] (a) Y. Ito, Y. Inubushi, T. Saegusa, *Synth. Commun.* **1974**, *4*, 289; (b) Y. Ito, Y. Inubushi, T. Saegusa, *Tetrahedron Lett.* **1974**, *15*, 1283.

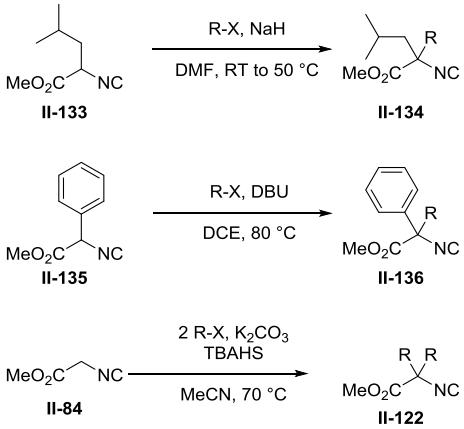
[159] S. Kojima, H. Ohkawa, T. Hirano, S. Maki, H. Niwa, M. Ohashi, S. Inouye, F. I. Tsuji, *Tetrahedron Lett.* **1998**, *39*, 5239. (b) M. Muselli, L. Colombeau, J. Hédouin, C. Hoarau, L. Bischoff, *Synlett* **2016**, *27*, 2819. (c) X. He, A. F. Bell, P. J. Tonge, *Org. Lett.* **2002**, *4*, 1523.



Scheme 122: Azlactone to imidazolone.

α,α-Disubstituted isocyanoacetate synthesis

In order to construct different imidazolones with our silver-(I) nitrate-catalyzed reaction with α,α-disubstituted isocyanoacetate **II-12** and primary amine **II-72**, different α,α-disubstituted isocyanoacetates (**II-134**, **II-136** and **II-122**) were synthesized. By simply converting natural or unnatural α-amino acids to α-isocyanoacetates with an esterification/formylation/dehydration sequence, alkylation of α-monosubstituted or α-unsubstituted isocyanoacetate was possible under appropriate conditions (Scheme 123).

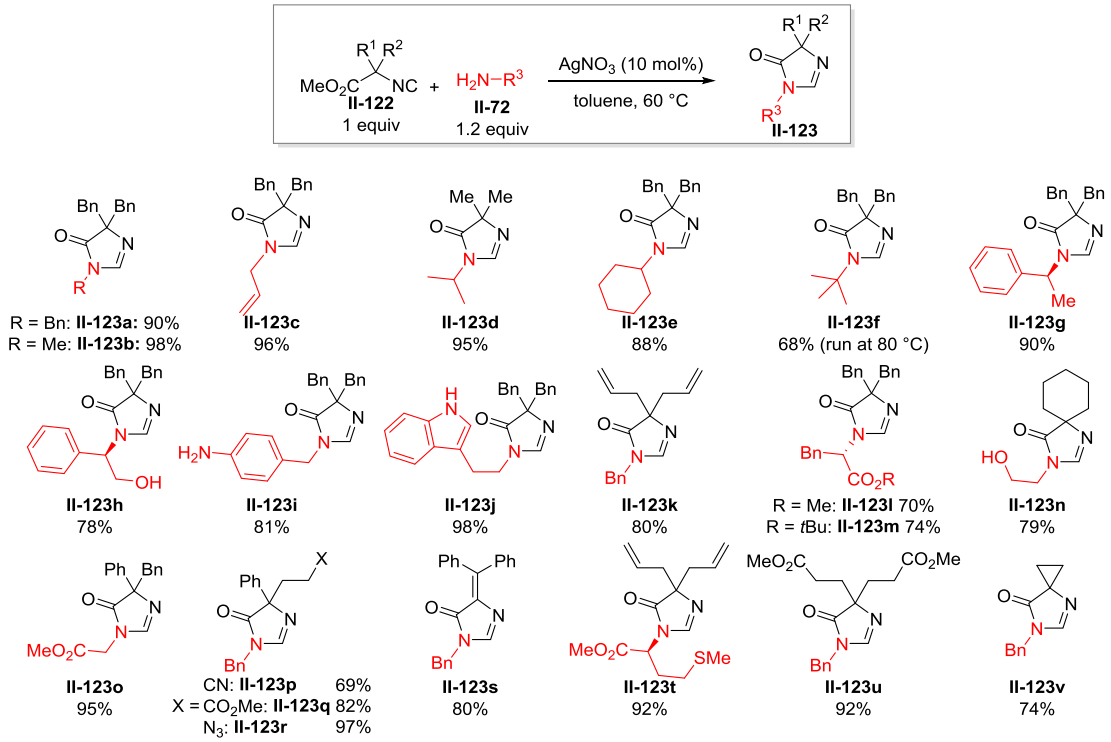


Scheme 123: Alkylation of mono or non α-substituted isocyanoacetate.

Scope of the reaction

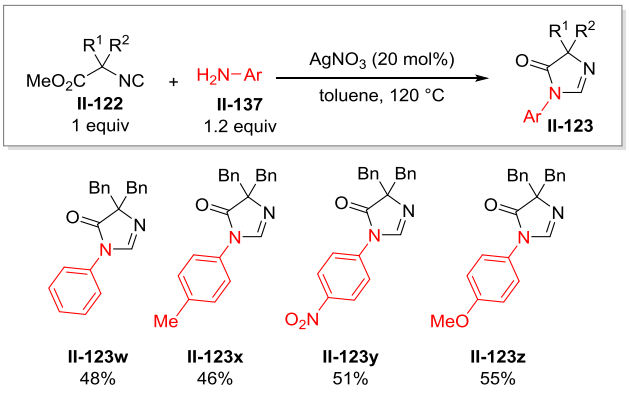
With the optimal conditions previously described, the scope and the functional-group tolerance of the reaction were inspected (Scheme 124). Various alkyl amines, linear, branched including sterically demanding *tert*-butylamine, reacted with methyl α,α-dibenzyl-α-isocyanoacetate **II-122a** to afford the corresponding imidazolones in excellent yields (**II-123a** to **II-123f**) Functionalized amines such as allylamine (**II-123c**), tryptamine (**II-123j**), enantioenriched α-amino esters (**II-123l** and **II-123s**), chiral amine (**II-123g**), unprotected amino alcohols (**II-123h** and **II-123m**) participated well in this reaction. Note that even thioether, known to have high affinity with silver, was compatible with our reaction conditions (**II-123s**). Different functional groups (CO_2Me, CN, N_3, olefin) on the α-isocyanoacetates were well tolerated (**II-123o to II-123q**, **II-123u**). Spiroimidazolones (**II-123m** and **II-123v**) can also be prepared without event. Interestingly, reaction of 4-aminobenzyl amine with **II-122a** was highly chemoselective to afford **II-123i** (94% yield) in which the aniline nitrogen was untouched. 5-Diphenylmethylene imidazolone **II-123r**, an

analogue of GFP chromophore, can also be prepared from methyl 2-isocyano-3,3-diphenylacrylate.



Scheme 124: Scope of the silver-catalyzed isocyanide insertion.

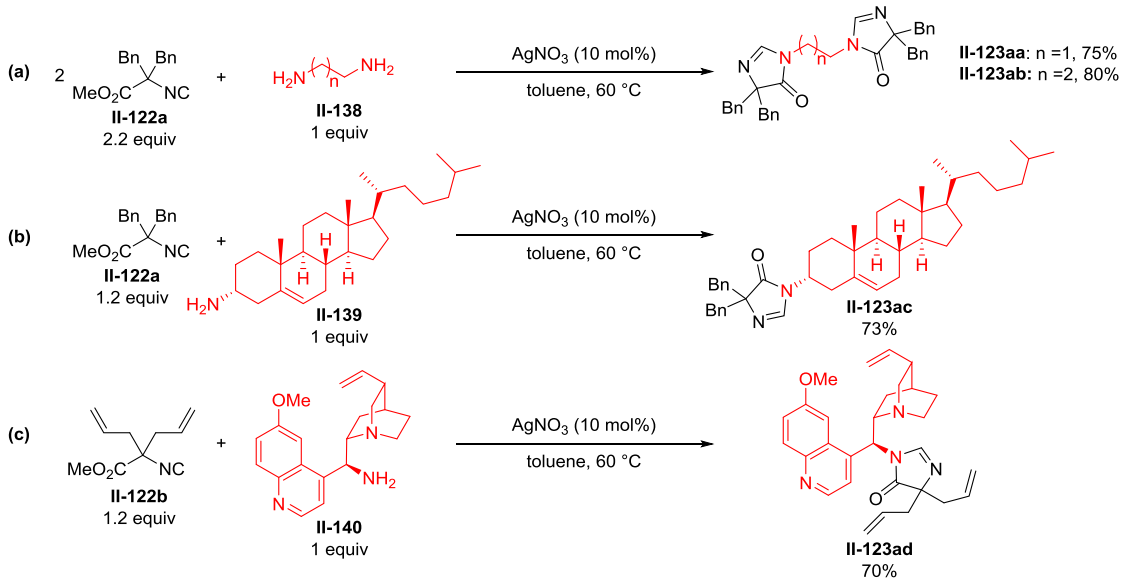
Aniline **II-137** derivatives have been tested as amine partner in our optimal condition reaction but no reaction was observed. However, by performing the reaction at higher temperature (120 °C) with 20 mol% of $AgNO_3$, the anilines **II-137** regardless its electronic nature participated in the reaction to afford the corresponding *N*-arylated imidazolones, albeit in moderate yields (**II-123w to II-123z**) (Scheme 125).



Scheme 125: Scope of the reaction with aniline as primary amine.

Reaction of diamines was also possible if two equivalents of disubstituted α-isocyanoacetate were used which afforded bis-imidazolones (**II-123aa** and **II-123ab**) in good yields (Scheme 126, **(a)**).

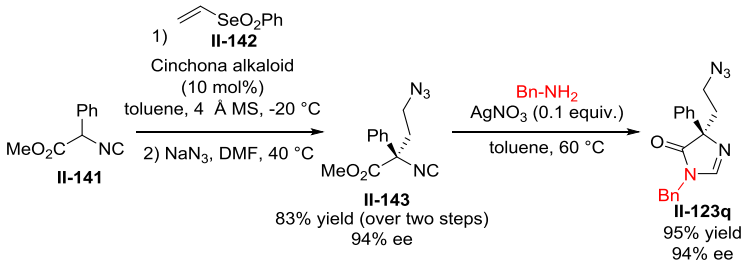
Finally, the protocol could also be applied to complex natural products. Thus, 3-α-amino-5-cholestene **II-139** and 9-amino quinidine **II-140** were converted to their imidazolone derivatives (**II-123ac** and **II-123ad**) in yields of 73% and 70%, respectively (Scheme 126 **(b)** & **(c)**). Derivatives of 3-amino-5-cholestene were important cellular probes with potential medical applications.[160] We believed that such a late stage functionalization protocol could be a useful synthetic tool in medicinal chemistry.



Scheme 126: Late stage imidazolone synthesis on complex molecules.

The synthesis of enantioenriched 3,5,5-trisubstituted imidazolone **II-123q** has been achieved by following two methodologies developed in our lab (Scheme 127).[14] Firstly, the enantioselective organocatalytic Michael addition/S_N2 sequence offered the azide compound **II-143** in 83% yield over two steps with 94% *ee*. Then, the application of our silver catalyzed transformation allowed the formation of the enantioenriched 3,5-(*R*)-5-imidazolone derivative **II-123q** in 95% yield with 94% *ee*.

[160] S. Boonyarattanakalin, J. Hu, S. A. Dykstra-Rummel, A. August, B. R. Peterson, *J. Am. Chem. Soc*. **2007**, *129*, 268.

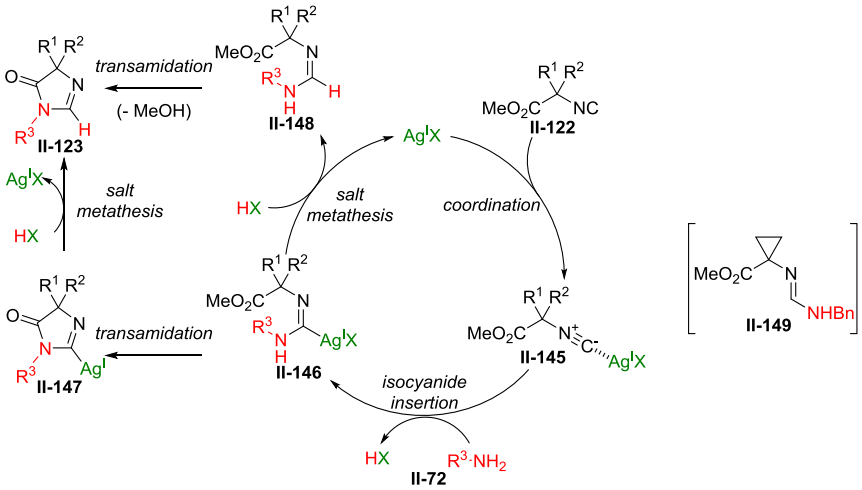


Scheme 127: Enantioenriched α,α-disubstituted imidazolone synthesis.

Suggested mechanism

A possible reaction pathway was shown in Scheme 128. Coordination of isocyanides and amine to silver would afford the complex **II-145**. Migratory insertion from **II-145** would afford **II-146** and HX which would undergo salt metathesis to produce amidine **II-148** with concurrent regeneration of the silver salt. Intramolecular lactamization of **II-148** would then furnish the observed product **II-123**. Another pathway where the metalated amidine **II-146** underwent amidation followed by salt metathesis to afford the desired compound could also be considered.

We note that no reaction took place in the absence of silver nitrate and that the formation of amidine **II-149** was clearly observed by ^{1}H NMR when the reaction was performed at 40 °C under otherwise standard conditions.

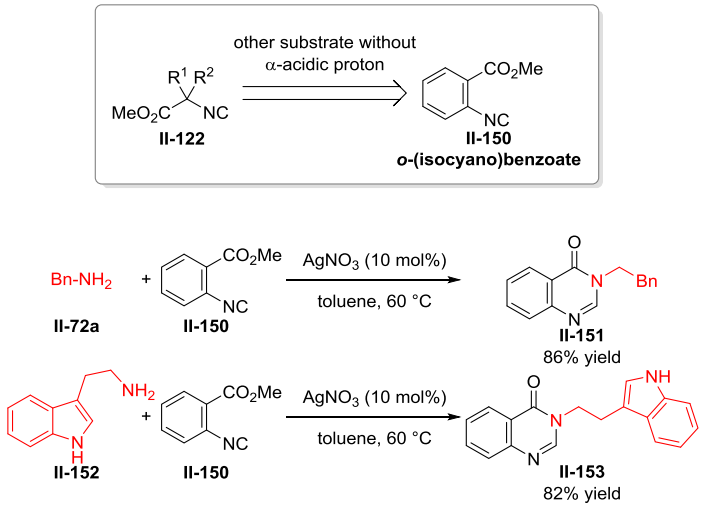


Scheme 128: Suggested mechanism of silver-catalyzed isocyanide insertion/lactamization.

Methyl o-isocyanobenzoate as partner

Methyl *o*-isocyanobenzoate **II-150**, another isocyanide substrate without α-acid proton, has been used in the presence of a catalytic amount of $AgNO_3$ and primary amine **II-72** (Scheme 129). Unsurprisingly, 3-substituted quinazolin-4(3H)-one **II-151**, a privileged scaffold in medicinal chemistry, was obtained in good yield. For example, when benzylamine

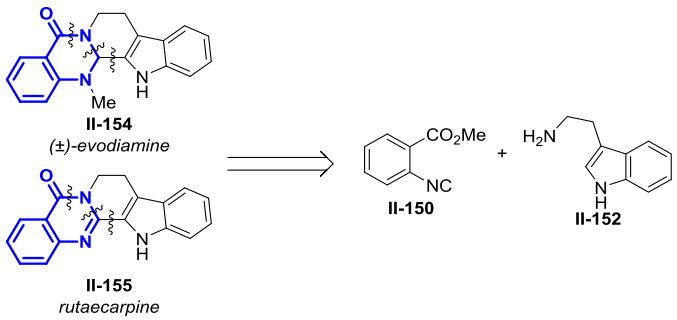
II-72a or tryptamine **II-152** were mixed with methyl *o*-isocyanobenzoate **II-150**, the respective quinazolin-4(3H)-one **II-151** and **II-153** were isolated in 86% and 82% yield.



Scheme 129: Application of the silver-catalyzed isocyanide insertion for quinazolin-4-one synthesis.

Application for natural product synthesis

Evodiamine **II-154** and rutaecarpine **II-155** are quinazolinecarboline alkaloids isolated from the dried fruit of *evodia rutaecarpa*, a plant used in traditional Chinese medicine against headache, dysentery, cholera, etc.[161] Due to the medicinal importance of these alkaloids, various synthetic routes have been developed.[162] With the presence of quinazolin-4(3H)-one moiety in the two natural products, the syntheses of evodiamine **II-154** and rutaecarpine **II-155** have been chosen to illustrate our methodology (Scheme 130).

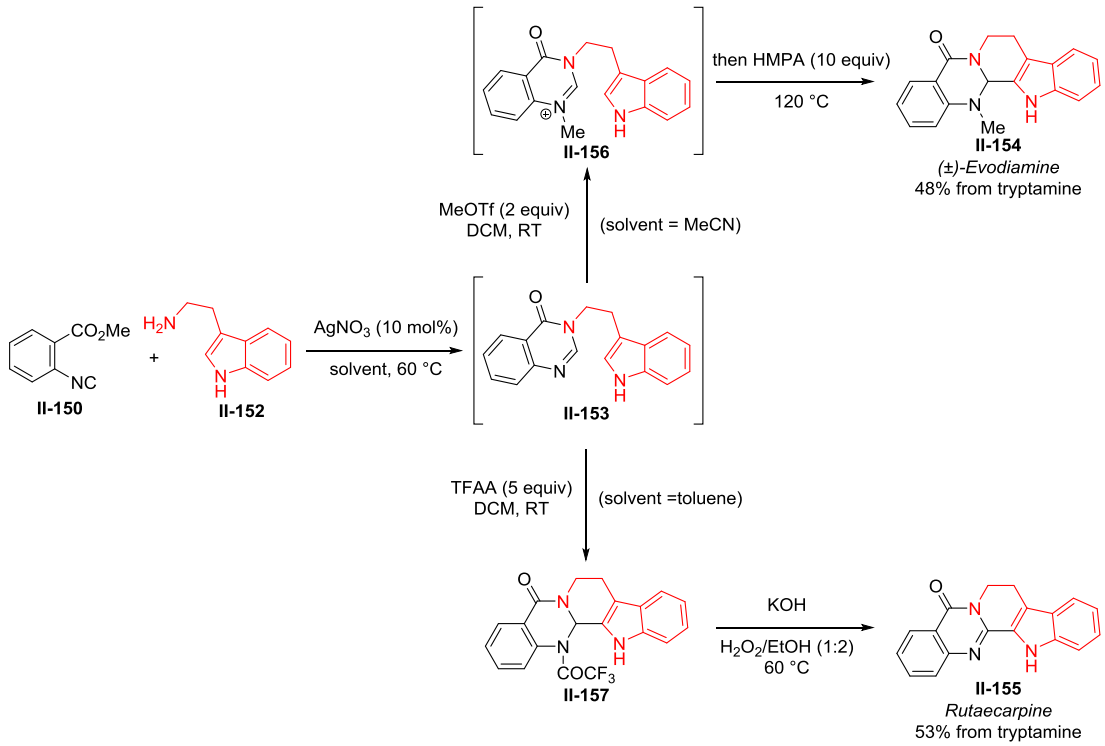


Scheme 130: Retrosynthesis of evoadiamine and rutaecarpine.

Silver nitrate-catalyzed condensation of tryptamine **II-152** with methyl isocyanobenzoate **II-150** afforded quinazolinone **II-153**. Compound **II-153**, without purification, was methylated with methyl triflate to afford *N*-methylated intermediate **II-156**. Adding HMPA to the reaction mixture and heating the solution to 120 °C promoted the

[161] T. Wang, Y. Wang, Y. Kontani, Y. Kobayashi, Y. Sato, N. Mori, H. Yamashita, *Endocrinology*. **2008**, *149*, 358.
[162] S. H. Lee, J.-K. Son, B. S. Jeong, T.-C. Jeong, H. W. Chang, E.-S. Lee, Y. Jahng, *Molecules* **2008**, *13*, 272.

Pictet-Spengler reaction and furnished (±)-evodiamine **II-154** in 49% overall yield. On the other hand, treatment of **II-153** with TFAA afforded **II-157** which, upon treatment with hydrogen peroxide under basic conditions for an oxidation and deprotection step, provided rutaecarpine **II-155** in 53% overall yield (Scheme 131).



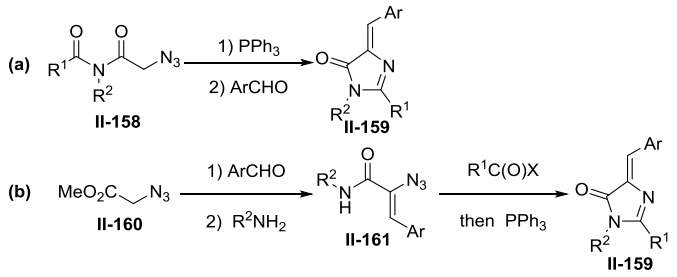
Scheme 131: Rutaecarpine & (±)-Evodiamine synthesis.

2,3,5,5-Tetrasubstituted imidazolone synthesis

The 2,3,5,5-tetrasubstituted imidazolone cores are important compound with fluorescent properties. Contained in the Kaede protein,[163] a photoactivatable fluorescent macromolecule, or in the BODIPY-like Burgess fluorophore,[155c] this moiety has been synthetized by means of different synthetic methodologies.

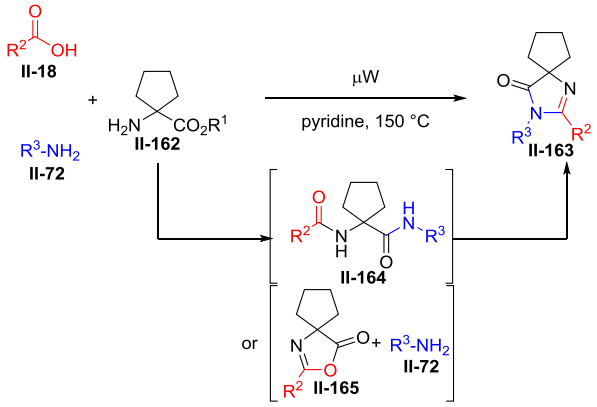
One of the approaches has been reported via an aza-Wittig cyclization/Knoevenagel condensation and afforded C-2 substituted imidazole **II-159** in good yield (Scheme 132, **(a)**). Knoevenagel condensation could also happen before the aza-Wittig cyclization to deliver the same type of heterocycle **II-159** (Scheme 132, **(b)**). [164,155c,165]

[163] I. V. Yampolsky, A. A. Kislukhin, T. T. Amatov, D. Shcherbo, V. K. Potapov, S. Lukyanov and K. A. Lukyanov, *Bioorg. Chem.* **2008**, *36*, 96.
[164] H. Takeuchi, S. Hagiwara, S. Eguchi, *Tetrahedron* **1989**, *45*, 6375; (b) Y. A. Ortiz Barbosa, D. J. Hart, N. A. Magomedov, *Tetrahedron* **2006**, *62*, 8748.
[165] M. S. Baranov, K. M. Solntsev, K. A. Lukyanov, I. V. Yampolsky, *Chem. Commun.* **2013**, *49*, 5778.



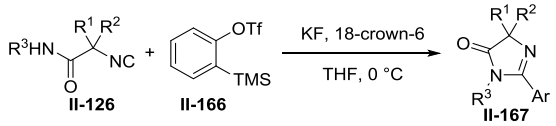
Scheme 132: Aza-Wittig cyclization.

Three-component reaction of of α-aminoester **II-162**, carboxylic acid **II-18** and primary amine **II-72** under microwave irradiation afforded compound **II-163**. the compound **II-163** was formed via diamide **II-164** or azlactone **II-165** intermediate in moderate to good yield (Scheme 133).[166]



Scheme 133: Microwave 3-CR using α,α-disubstituted aminoester, primary amine and carboxylic acid.

Recently, Pirali *et al* have developed a convergent one-pot synthesis of 2-arylated imidazolones **II-167** from the reaction of α-isocyanoacetamides **II-126** with benzynes **II-166**. This [4+1] heteroannulation involved the *in situ* formed aryne intermediate (Scheme 134).[167]

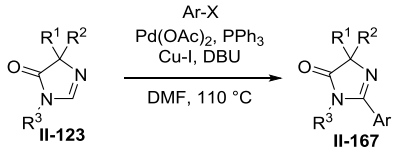


Scheme 134: [4+1] Cyclization if α-isocyanoamide and arynes.

Hoarau, Bischoff and coworkers have also reported a direct C2-H functionalization of imidazolones **II-123** using palladium-(0) and copper-(I) as bimetallic catalytic system. In their

[166] (a) P. Ye, K. Sargent, E. Stewart, J.-F. Liu, D. Yohannes, L. Yu, *J. Org. Chem.* **2006**, *71*, 3137.
[167] A. Gesù, C. Pozzoli, E. Torre, S. Aprile, T. Pirali, *Org. Lett.* **2016**, *18*, 1992.

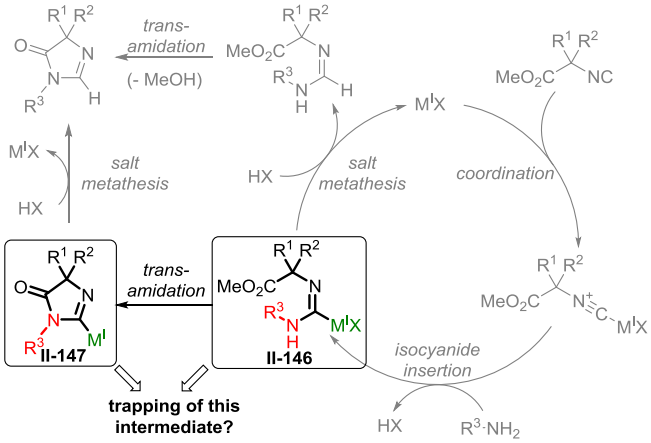
reaction, the presence of a base was primordial and DBU gave the best result to afford the 2,3,5,5-tetrasubstituted imidazole **II-167** (Scheme 135).[168]



Scheme 135: C-H activation of C-2 unsubstituted imidazole.

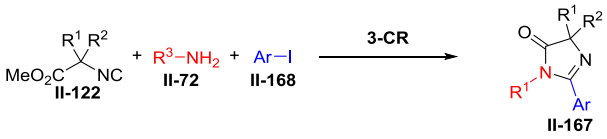
Development of three component reaction

In our suggested mechanism (Scheme 128), we depicted two possible metalated species (**II-147** and **II-146**) where the metal was carried by the carbon of the former isocyanide. By taking advantage of **II-147** and **II-146**, we hoped to design a three component reaction where one of the intermediate could be trapped for the rapid C-2 functionalization of the imidazolone compound.



Scheme 136: Suggested metalated intermediates in the silver-catalyzed transformation.

Keeping this in mind, we thought to develop a synthesis of 2,3,5,5-tetrasubstituted imidazolone **II-167** by reaction of α,α-disubstituted-α-isocyanoacetate **II-122**, primary amine **II-72** and aryl halide **II-168** (Scheme 137).



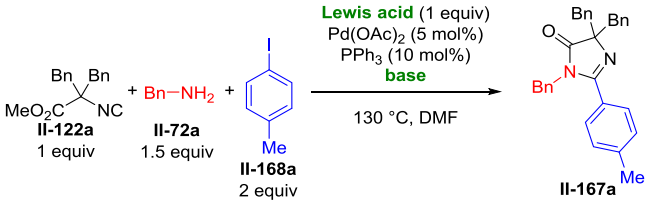
Scheme 137: 3-CR for the synthesis of 2,3,5,5-tetrasubstituted imidazolone.

[168] (a) M. Muselli, C. Baudequin, C. Hoarau, L. Bischoff, *Chem. Commun.* **2015**, *51*, 745. (b) M. Muselli, C. Baudequin, C. Perrio, C. Hoarau, L. Bischoff, *Chem. Eur. J.* **2016**, *22*, 5520.

Optimization of the 3-CR reaction

We chose **II-122a** (R1 = R2 = Bn), benzylamine **II-72a** and 4-methylphenyliodide **II-168a** as test substrates. Initial screening using $Pd(OAc)_2$ as transition metal catalyst, DBU as base and PPh_3 as ligand in DMF at 130 °C (Table 20). Combining this conditions with $AgNO_3$ afforded a complex reaction mixture (Entry 1). AgOTf and $Yb(OTf)_3$ afforded the desired product in low yield (Entry 2 and 3) whereas the combination of copper-(I) salt and $Pd(OAc)_2$ turned out to be more rewarding. The conditions used by Hoarau[168a], where copper iodide was used, gave the imidazolone **II-168a** in 68% NMR yield (Entry 5). Without DBU, the formation of imidazolone was still occurring and finally, the imidazolone **II-167a** could be formed in 72% isolated yield (75% NMR yield, Entry 7) when 1 equivalent of Cu^{I}_2O was mixed with $Pd(OAc)_2$. It was notable that, with copper-(II) salt or without Lewis acid (Entry 12 & 13), the yield of the desired heterocycle **II-167a** has decreased drastically.

Table 20: Lewis acid screening.

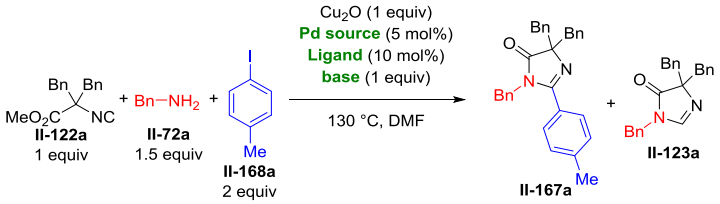


Entry	Lewis Acid	Base	NMR yield
1	$AgNO_3$	DBU	degradation
2	AgOTf	DBU	33%
3	$Yb(OTf)_3$	DBU	23%
4	$Cu^{I}I$	DBU	68%
5	$Cu^{I}I$	-	57%
6	$Cu^{I}Cl$	-	55%
7	Cu^{I}_2O	-	75% (72%)
8	$[Cu^{I}OTf]_2$.toluene (0.5 equiv)	-	58%
9	$Cu^{I}OAc$	-	21%
10	$[(MeCN)_4Cu^{I}]PF_6$	-	51%
11	$[(MeCN)_4Cu^{I}]BF_4$	-	50%
12	$Cu^{II}(OTf)_2$	-	6%
13	None	-	21%

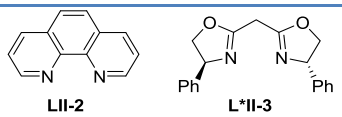
Different bases were used (Table 21, Entry 1 to 4). None of them were able to increase the yield of the reaction. Other palladium sources and ligands were also screened (Entry 5 to 8). Palladium-(0) complexes such as $Pd(dba)_2$ or $Pd(Ph_3)_4$ gave good outcome even if the $Pd(OAc)_2/PPh_3$ combination offered the best result. Unfortunately, only a complex mixture was obtained with phenanthroline as ligand (Entry 7). With (Py)-Box as ligand, imidazolone **II-167a** was obtained in 63% NMR yield (Entry 8).

Decreasing the Pd loading to 2 mol% under otherwise identical conditions afforded trisubstituted inidazolone II-123a in 26% yield accompanied by a trace amount of 2,3,5,5-tetrasubstituted imidazolone **II-167a**.

Table 21: Base/Palladium source screening.

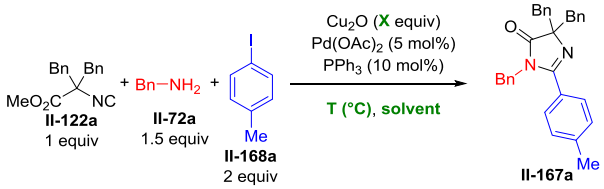


Entry	Pd source	Ligand	Base	NMR yield
1*	$Pd(OAc)_2$ (5 mol%)	PPh_3 (10 mol%)	-	75%
2	$Pd(OAc)_2$ (5 mol%)	PPh_3 (10 mol%)	DBU	28%
3	$Pd(OAc)_2$ (5 mol%)	PPh_3 (10 mol%)	Et_3N	57%
4	$Pd(OAc)_2$ (5 mol%)	PPh_3 (10 mol%)	Cs_2CO_3	27%
5	$Pd(dba)_2$ (5 mol%)	-	-	66%
6	$Pd(PPh_3)_4$ (5 mol%)	-	-	64%
7	$Pd(OAc)_2$ (5 mol%)	LII-2 (10 mol%)	-	messy
8	$Pd(OAc)_2$ (5 mol%)	L*II-3 (10 mol%)	-	63%
9	$Pd(OAc)_2$ (2 mol%)	PPh_3 (4 mol%)	-	7% + 26% X
10	$Pd(OAc)_2$ (10 mol%)	PPh_3 (20 mol%)	-	63%



Finally, the temperature, the solvent and the amount of copper-(I) oxide were examined (Table 22). 130 °C, DMF and 1 equivalent of copper salt gave the best result leading to the imidazolone **II-167a** in 75% yield.

Table 22: Fine tuning of the reaction.



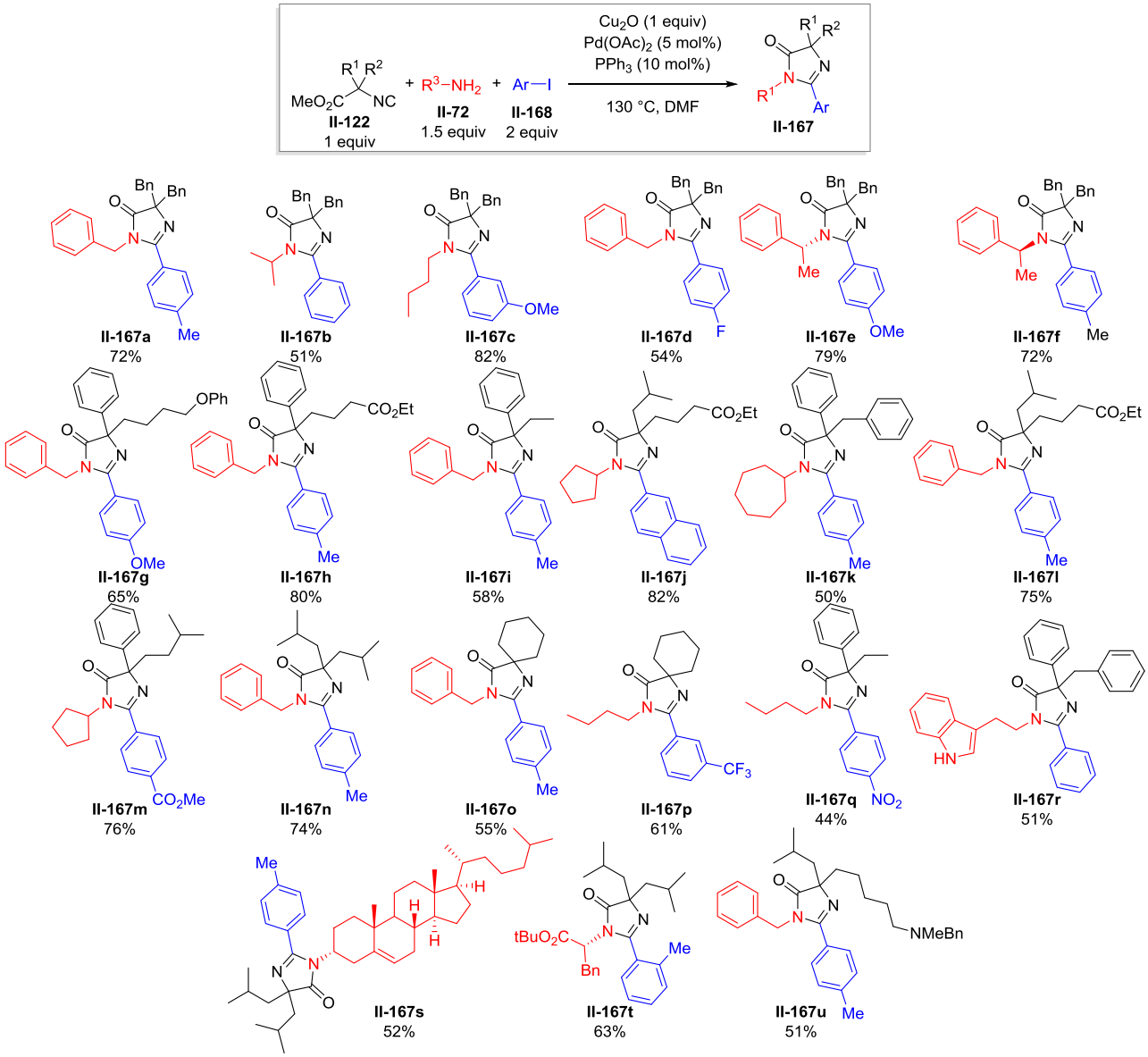
Entry	T (°C)	Solvent	Cu_2O (X equiv)	NMR yield
1*	130 °C	DMF	1 equiv	75%
2	110 °C	DMF	1 equiv	66%
3	150 °C	DMF	1 equiv	66%
4	130 °C	DMSO	1 equiv	41%
5	130 °C	DMF	0.1 equiv	34%
6	130 °C	DMF	0.25 equiv	54%
7	130 °C	DMF	0.5 equiv	69%

Scope of the 3-CR reaction

The novel three-component reaction displayed a broad application scope (Scheme 138). Aryl iodides bearing electron-donating (OMe **II-167c**, **II-167e and II-167g**) and electron-withdrawing groups (F **II-167d**; CO_2Me **II-167m**; CF_3 **II-167p**; NO_2 **II-167q**) were appropriate substrates for this reaction. Compound **II-167j** containing β-naphtyl at the C-2 position of the heterocycle could also be made by this methodology. Note that the position (*ortho*, *meta* or *para*) of the substituent on the C-2 aryl counterpart was not affecting the reaction.

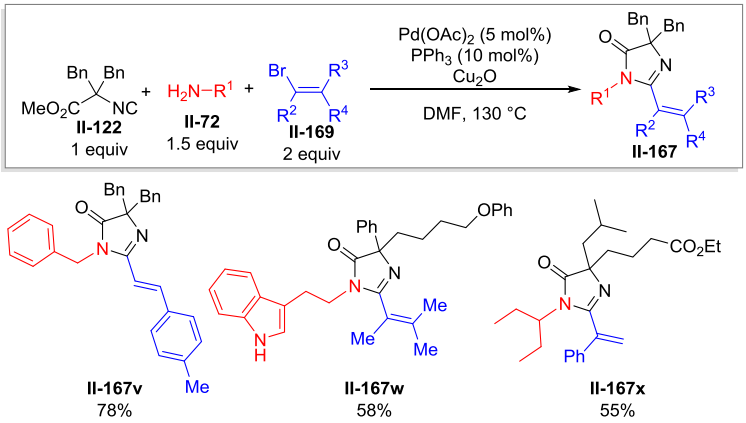
Functionalized amines such as tryptamine (**II-167r**), linear (**II-167a** and **II-167c**), branched (**II-167b**) and cyclic amine (**II-167j**, **II-167k** and **II-167m**) participated in this reaction without event. Reaction of (*R*)- and (*S*)-1-phenylethylamine with **II-122** and **II-168** afforded chiral imidazolones **II-167e** and **II-167f**, respectively, without epimerization. Chiral primary amine derived from the chiral pool such as the amino-cholesterol derivative **II-139** and phenylalanine *t*-Bu ester, were also accepted in this reaction and gave enantiopure scaffolds in one step in 52% (**II-167s**) and 63% (**II-167t**) isolated yield respectively.

The use of cyclohexyl α-isocyanonacetate **II-122** in this reaction allowed the formation of C-2 substituted spiroimidazolones **II-167o** and **II-167p**. Finally, aryl and alkyl chain with functionalities (-OPh, $-CO_2Me$, -NMeBn) on the α,α-disubstituted α-isocyanoacetate partner were also allowed in this transformation (**II-167g**, **II-167h**, **II-167j**, **II-167l** and **II-167u**).



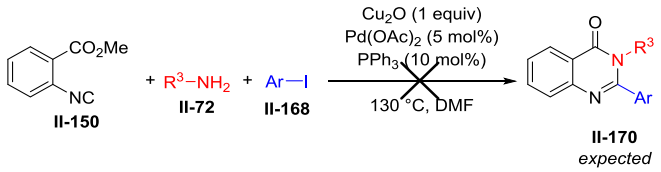
Scheme 138: Scope of the three component reaction with aryl iodide.

Vinylbromides, including 1,2-disubstituted, 1,1-disubstituted and tetra-substituted ones, reacted smoothly with **II-122** and **II-169** to provide 2-vinyl substituted imidazolones **II-167v**, **II-167w** and **II-167x** in good yields (Scheme 139).



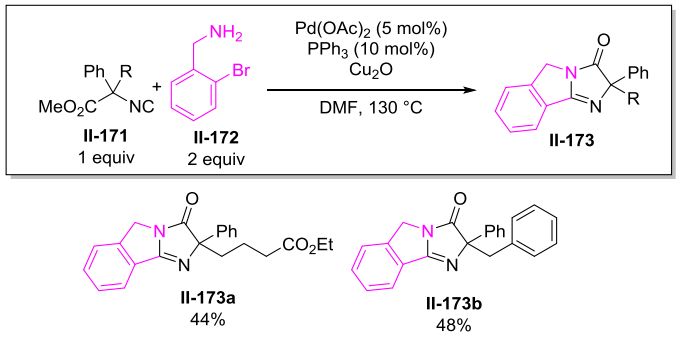
Scheme 139: Scope of the three-component reaction with alkenyl halide.

In order to reach different interesting scaffolds, the reaction conditions have been applied to methyl *o*-isocyanobenzoate **II-150**. Unfortunally, degradation of the starting materials was observed (Scheme 140). This was probably due to the easy and known polymerization of this type of isocyanide.



Scheme 140: 2,2-Disubstituted-2,5-dihydro-3H-imidazo[2,1-a]isoindol-3-one synthesis.

Based on this novel reaction sequence, more complex domino processes could be designed for the one-pot synthesis of polyheterocyclic compounds. For example, reaction of (2-bromophenyl)methanamine **II-172** with methyl isocyanoacetate **II-171**furnished tricyclic compounds **II-173a** and **II-173b**, respectively (Scheme 141).



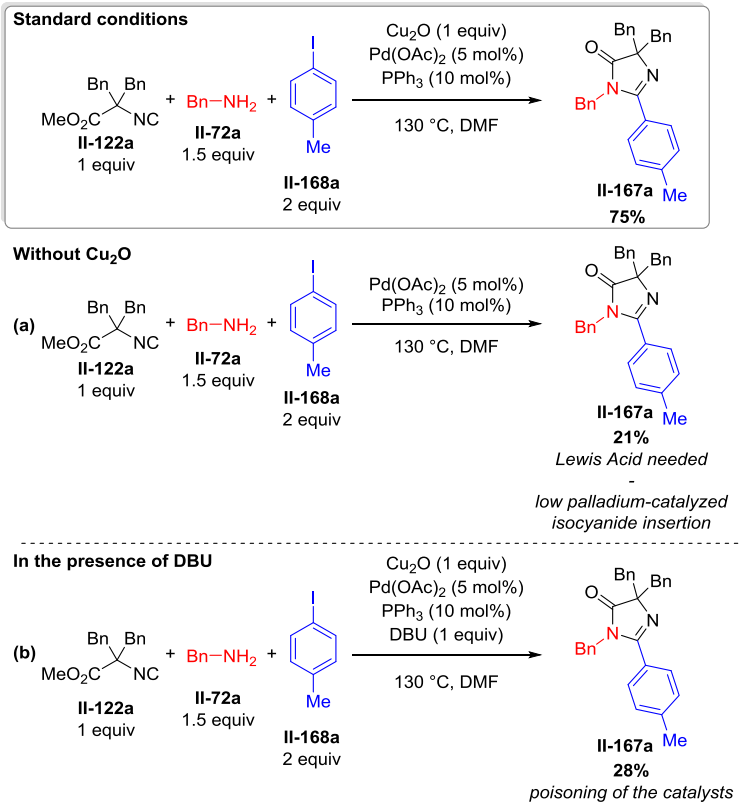
Scheme 141: Bimetallic catalyzed 3-CR with methyl *o*-isocyanobenzoate.

Mechanistic study

In this 3 component reaction, several pathways were possible to reach the desired 2,3,5,5-tetrasubstituted imidazolone **II-167**. As initial step, we suggested that the reaction

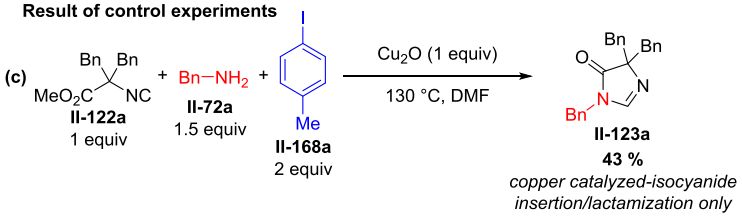
started with isocyanide insertion. Palladium and copper, the two metals present in our reaction, are known to promote this type of reaction. Without copper, the yield for the imidazolone formation dropped considerably which highlighted the importance of the Lewis acid (Scheme 142, **(a)**).

If a base was added in our standard conditions, an important drop of the yield was also observed (Scheme 142, **(b)**). With DBU, the heterocycle was formed in 28% yield. In the methodology developped by Hoarau (Scheme 135),[168] the presence of a base was primordial to promote the C-H activation of the 3,5,5-trisubstituted imidazolone **II-123**. In our case however, the base seemed to poison the bimetallic catalytic system.



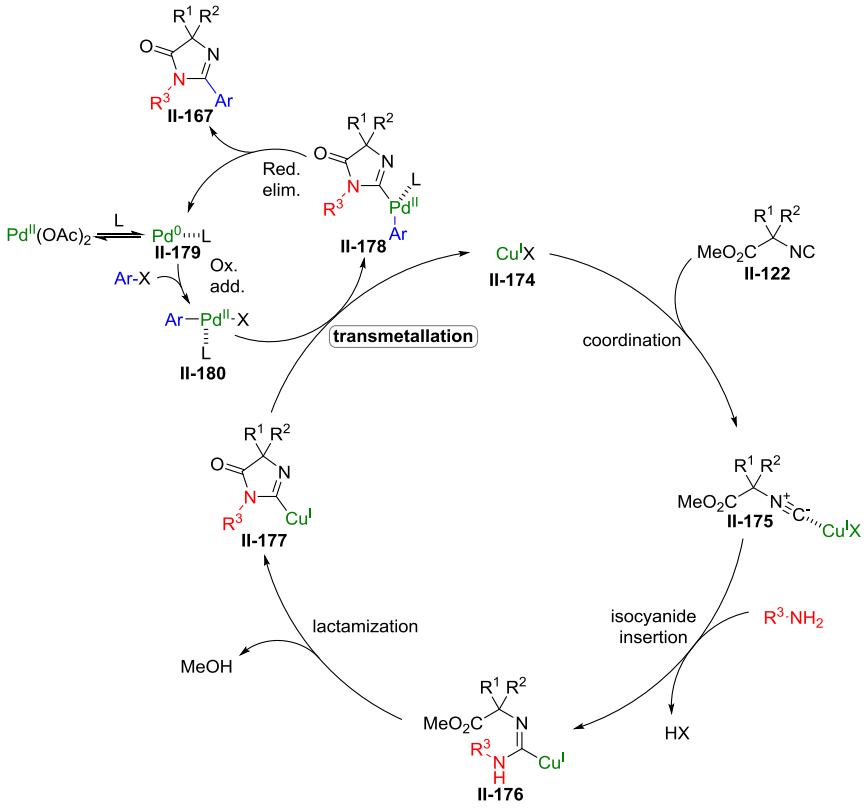
Scheme 142: Importance of the reagents.

In the absence of palladium and triphenylphosphine, the formation of the C-2 substituted **II-167a** was not observed (Scheme 143). Unsurprisingly, with only Cu_2O as catalyst, the product **II-123a** was formed via isocyanide insertion/lactamization process in 43% yield.



Scheme 143: Importance of the palladium acetate.

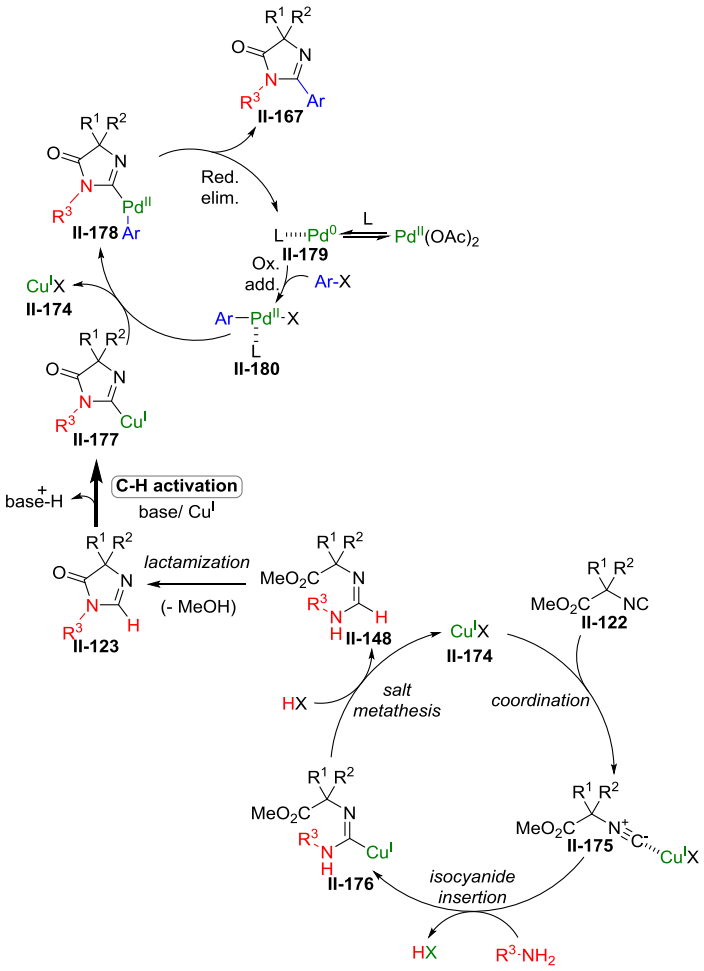
Two plausible mechanisms were depicted in Scheme 144 and Scheme 145 respectively. In the Scheme 144, the mechanism began with a coordination/isocyanide insertion sequence to afford the metalated amidine **II-176**. After lactamization to deliver **II-177**, the transmetallation of the copper-(I) species **II-178** with the palladium-(II) **II-180** gave the cyclic intermediate **II-178** with regeneration of the copper-(I) salt **II-174**. Final reductive elimination offered the tetrasubstituted imidazolone **II-167** and the recovery of the palladium-(0) **II-179**. In this mechanism, we suggested that the isocyanide insertion set the copper on the molecule which permited the transmetallation with the palladium intermediate **II-180**.



Scheme 144: Transmetalation pathway.

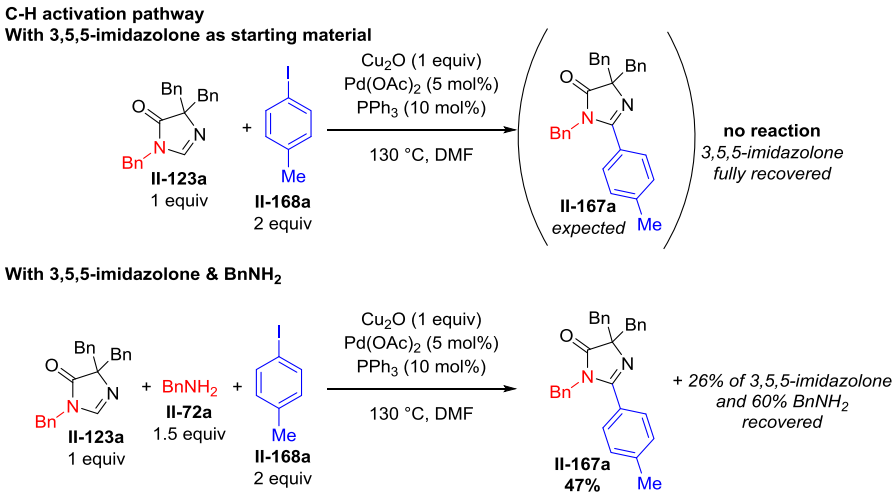
For the mechanism proposed in Scheme 145, the first catalytic cycle correspond to the suggested Lewis acid-catalyzed cycle described for the synthesis of trisubstituted imidazolone **II-123** (Scheme 128). Then, a C-H activation of the C-2 position (generally in the presence of

a base and a Lewis acid) of **II-123** gave the compound **II-177**. After metal exchange, the palladated intermediate **II-178** was formed. Reductive elimination delivered the product **II-167** and the regeneration of **II-179**. In this pathway, basic conditions were needed to deprotonate the C-2 of the imidazolone **II-123** (organic base or the counter anion of the salt).



Scheme 145: C-H activation pathway.

In order to legitimate one pathway to the other in this mechanism, the reaction conditions (1 equiv Cu_2O, 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 130 °C, DMF) were applied to the unsubstituted C-2 imidazolone **II-123a** and *p*-iodotoluene **II-168a**. Interestingly, no reaction was observed and the trisubstituted imidazolone **II-123a** was fully recovered even after 12 hours (Scheme 146, **(a)**). The same experiment was run with 1.5 equivalent of benzyl amine. This time, the reaction offered the tetrasubstituted **II-167a** in 47% NMR yield with 26% NMR yield of **II-123a** (Scheme 146, **(b)**).



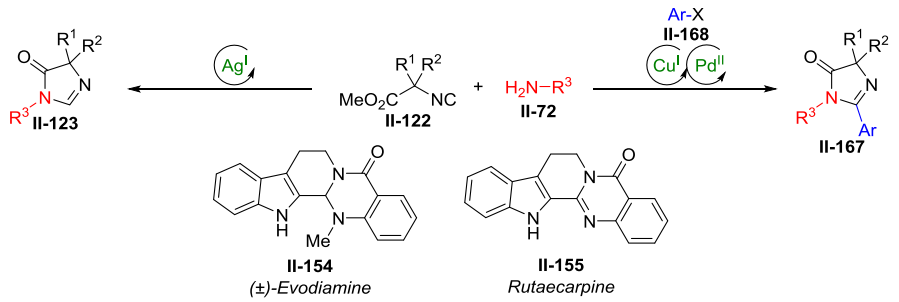
Scheme 146: Other experiment on the C-H pathway.

These two experiments have shown that a base was needed to activate the C-H bond of the C2 of the imidazolone **II-123a**. Without base, the C-H activation proposed in the Scheme 145 could not occur and rendered impossible the C-2 metalation of the imidazolone (intermediate **II-177**).

These observations did not allow the discrimination of one of the two pathways. The reaction could go via the C-H activation pathway (Scheme 145) if the benzyl amine was playing the role of base. The mechanism described in Scheme 144 could also occur and the copper-catalyzed isocyanide insertion into the amine could deliver the C-2 metalated 5-membered heterocycle **II-177** for the transmetalation step with **II-180**.

Conclusion

The syntheses of various 3,5,5-trisubstituted imidazolones **II-123** and 2,3,5,5-tetrasubstituted imidazolones **II-167** have been achieved. Two different methodologies have been developed by taking advantage of the rich chemistry of the isocyanide group. Firstly, α,α-disubstituted isocyanoacetate **II-122** with primary amines **II-72** in the presence of a catalytic amount of $AgNO_3$ afforded 3,5,5-trisubstituted imidazolones **II-123** in good to excellent yields. This unprecedented domino isocyanide/amine insertion followed by lactamization occurred under mild condition (toluene, 60 °C). Secondly, reaction of α,α-disubstituted isocyanoacetate **II-122** with primary amines **II-72** and aryl halide **II-168** in the presence of Cu^{I}/Pd^{II} bimetallic system provided 2,3,5,5-tetrasubstituted imidazolone **II-167** via formation of one C-C bond and two C-N bonds in moderated to good yield. Finally the concise synthesis of two natural product, rutaecarpine **II-154** and (±) evodiamine **II-155**, have been accomplished to illustrate the utility of this chemistry.[169]



Scheme 147: Summary of the isocyanide insertion of α,α-disubstituted isocyanoacetate into primary amine - Development of 3 CR reaction and application in natural product synthesis.

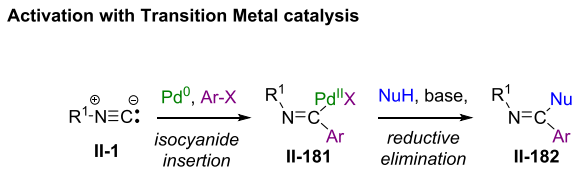
[169] (a) A. Clemenceau, Q. Wang, J. Zhu, *Org. Lett.* **2017**, accepted; (b) A. Clemenceau, Q. Wang, J. Zhu, *manuscript in preparation.*

Chapter 4: Palladium-Catalyzed Insertions of *o*-Isocyanobenzonitrile and 2-Substituted 3-Cyclopropyl-2-Isocyanopropanoate

Introduction

Since the explosion of palladium catalysis at the end of the last century, this type of chemistry has become one of the most prolific research areas in organic chemistry. In 2010 Heck, Negishi and Suzuki were even awarded by the Nobel Prize for their work on palladium-catalyzed cross couplings in organic synthesis. Today, this field is commonly applied at the industrial scale for the synthesis of important drugs by creating C-C, C-O or C-N bonds which where complicated to form before.[170]

Inspired by the previous work on palladium-catalyzed carbon monoxide insertion, Kosugi and Migita reported in 1986 the first palladium-catalyzed isocyanide insertion where *tert*-butyl isocyanide, bromobenzene and an organotin compound reacted together in the presence of $Pd^0(Ph_3)_4$.[171] More than ten years after, Whitby and coworkers observed that the use of non-toxic nucleophiles (amines, alcoholates, thiolates) instead of the organotin reagent was possible and offered different ketimine derivatives **II-182** in moderate to good yield using similar chemistry (Scheme 148).[172] [109c,109d,109e]



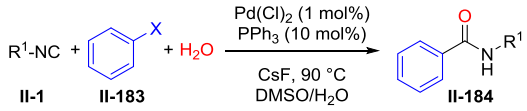
Scheme 148: Palladium-catalyzed isocyanide insertion.

Over the years, different methodologies have been developed taking advantage of this insertion step. In the palladium-catalyzed isocyanide insertion, the formation of aryl imidoyl-palladium intermediate **II-181**, which reacts further with a nucleophile, is the major difference with the Lewis acid-catalyzed isocyanide insertion in which a direct insertion into the heteroatom-H bond of the nucleophile is observed.

[170] C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062.
[171] M. Kosugi, T. Ogata, H. Tamura, H. Sano and T. Migita, *Chem. Lett.* **1986**, 1197 and references 1 to 3 cited in for palladium-catalyzed carbon monoxide insertion.
[172] C. G. Saluste, R. J. Whitby, M. Furber, *Angew. Chem. Int. Ed*. **2000**, *39*, 4156; (b) C. G. Saluste, R. J. Whitby, M. Furber, *Tetrahedron Lett.* **2001**, *42*, 6191; (c) R. J. Whitby, C. G. Saluste, M. Furber, *Org. Biomol. Chem.* **2004**, *2*, 1974; (d) K. K. R. Tetala, R. J. Whitby, M. E. Light, M. B. Hurtshouse, *Tetrahedron Lett.* **2004**, *45*, 6991; (e) C. G. Saluste, S. Crumpler, M. Furber, R. J. Whitby, *Tetrahedron Lett.* **2004**, *45*, 6995.

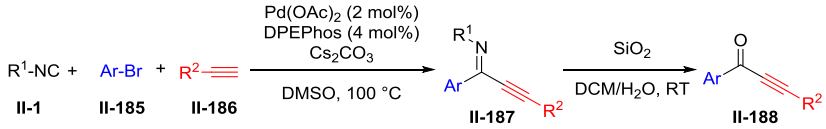
Trapping of imidoyl-Pd intermediates with other nucleophiles

In 2011, it has been reported that water could act as nucleophile to trap the imidoyl-palladium intermediate and afforded amides **II-184** in good yield.[173]



Scheme 149: Pd-catalyzed isocyanide insertion with water was nucleophile.

Palladium-catalyzed isocyanide insertion in the presence of terminal alkyne as nucleophile **II-186** was also developed. The subsequent alkynyl imine **II-187** could then be easily hydrolyzed to afford the ketone **II-188**.[174]

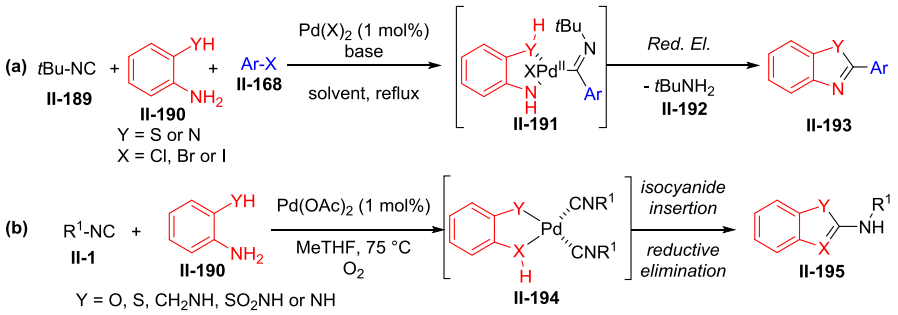


Scheme 150: Pd-catalyzed isocyanide insertion with terminal alkyne as nucleophile.

Bisnucleophiles have also been used with palladium and isocyanides. In the presence of aryl bromide **II-168**, the oxidative addition of the palladium followed by isocyanide insertion afforded the imidoyl-palladium intermediate. Then, the bisnucleophile **II-190** was incorporated after reductive elimination. Finally, the release of *tert*-butyl amine **II-192** at reflux gave C-2 arylated heterocycles **II-193** (Scheme 151, **(a)**)[175a].

In the absence of aryl halide **II-168** and base, Ruitjer and Orru reported the synthethis of C-2 aminated heterocycles using bisnucleophile **II-190** via Pd-catalyzed isocyanide insertion. In this case, it was proposed that the double oxidative addition in the bisnucleophile **II-190** gave the 5-membered palladacycle **II-194**, where at least two molecules of isocyanide were coordinated to the palladium. A sequence of isocyanide insertion and reductive elimination furnished finally various heterocycles **II-195** depending on the bisnucleophile used (Scheme 151, **(b)**).[176b]

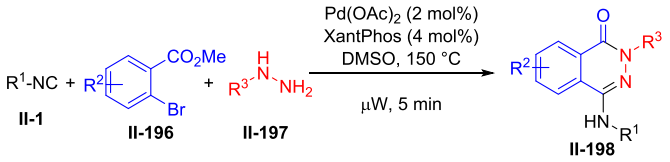
[173] H. Jiang, B. Liu, Y. Li, A. Wang, H. Huang, *Org. Lett.* **2011**, *13*, 1028.
[174] T. Tang, X.-D. Fei, Z.-Y. Ge, Z. Chen, Y.-M. Zhu, S.-J. Ji, *J. Org. Chem.* **2013**, *78*, 3170.
[175] (a) J. V. Geden, A. K. Pancholi, M. Shipman, *J. Org. Chem.* **2013**, *78*, 4158; V. N. Bochatay, P. J. Boissarie, J. A. Murphy, C. J. Suckling, S. Leng, *J. Org. Chem.* **2013**, *78*, 1471. (b) T. Vlaar, R. C. Cioc, P. Mampuys, B. U. W. Maes, R. V. A. Orru, E. Ruitjer, *Angew. Chem. Int. Ed.* **2012**, *51*, 13058.
[176] (a) J. V. Geden, A. K. Pancholi, M. Shipman, *J. Org. Chem.* **2013**, *78*, 4158; V. N. Bochatay, P. J. Boissarie, J. A. Murphy, C. J. Suckling, S. Leng, *J. Org. Chem.* **2013**, *78*, 1471. (b) T. Vlaar, R. C. Cioc, P. Mampuys, B. U. W. Maes, R. V. A. Orru, E. Ruitjer, *Angew. Chem. Int. Ed.* **2012**, *51*, 13058.



Scheme 151: Pd-catalyzed isocyanide insertion with bisnucleophile.

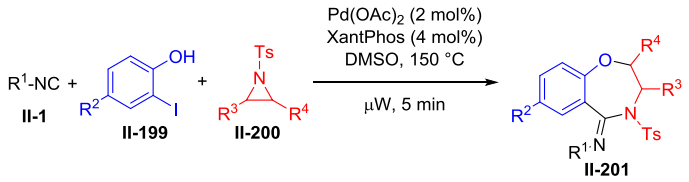
Domino reaction after classical Pd-isocyanide insertion

The inventiveness of the organic chemists and the broad applicability of Pd-catalyzed isocyanide insertions have allowed the design of different domino processes. An example has been described in 2011 with the palladium-catalyzed reaction of isocyanide **II-1**, methyl *o*-bromobenzoate **II-196** and hydrazine **II-197**. After Pd-catalyzed isocyanide insertion, the imidoyl palladium reacted with hydrazine. Then, the final lactamization delivered 4-aminophthalazin-1(2H)-ones **II-198**.[177]



Scheme 152: Pd-catalyzed domino reaction involving isocyanide insertion for the synthesis of 4-aminophthalazin-1(2H)-ones.

The Pd-catalyzed domino reaction of isocyanide **II-1**, *o*-iodophenol **II-199** and aziridine **II-200** has also been reported. In this transformation the imidoyl palladium was attacked by the nitrogen atom of the aziridine. The subsequent 3-membered ring opening gave the uncommon 7-membered ring **II-201** (Scheme 153).[178]

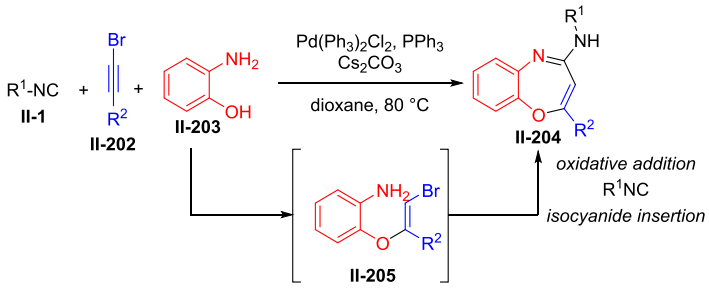


Scheme 153: Pd-catalyzed domino reaction involving isocyanide insertion and aziridine.

Another example of cascade transformation where bromoalkyne **II-202**, isocyanide **II-1** and *o*-aminophenol **II-203** were used together is depicted in Scheme 154. This reaction was

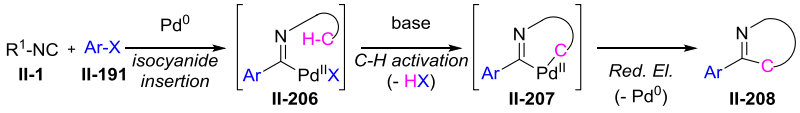
[177] T. Vlaar, E. Ruijter, A. Znabet, E. Janssen, F. J. J. De Kanter, B. U. W. Maes, R. V. A. Orru, *Org. Lett.* **2011**, *13*, 6496.
[178] F. Ji, M.-f. Lv. W.-b. Yi, C. Cai, *Adv. Synth. Catal.* **2013**, *355*, 3401.

presumably occurring via a vinyl palladium intermediate **II-205** which underwent isocyanide insertion. The final reductive elimination with incorporation of the amine offered the 7-membered heterocycle **II-204**.[179]



Scheme 154: Pd-catalyzed domino reaction involving isocyanide insertion involving bromoalkyne.

Palladium chemistry has been also applied for the activation of C-H bond. Several domino processes involving palladium-catalyzed isocyanide insertion and C-H activation reactions have been reported.[109g] In this type of transformation, after formation of the imidoyl palladium intermediate **II-206**, a C-H activation gave the palladacycle **II-207**. Final reductive elimination produced the product **II-208** with regeneration of Pd-(0) (Scheme 155). Examples of C-H activation with acidic proton,[180] C(sp^2)-H activation,[181] and C(sp^3)-H activation[182] have been reported.



Scheme 155: Pd-catalyzed isocyanide insertion followed by C-H activation.

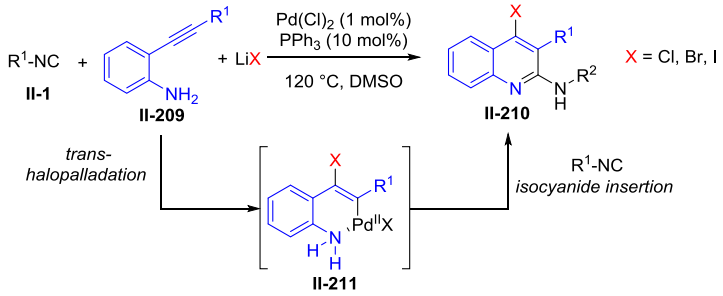
Palladium insertion into other bonds than C-X

Pd-catalyzed isocyanide insertion has been mostly described with oxidative addition as first step when the palladium-(0) is incorporated into a C-X bond of an alkenyl or aryl halide. However, insertion of palladium into other types of bonds is also known. In 2013, Jiang and Wu reported the palladium-catalyzed synthesis of 4-halo-2-aminoquinolines **II-210** using

---

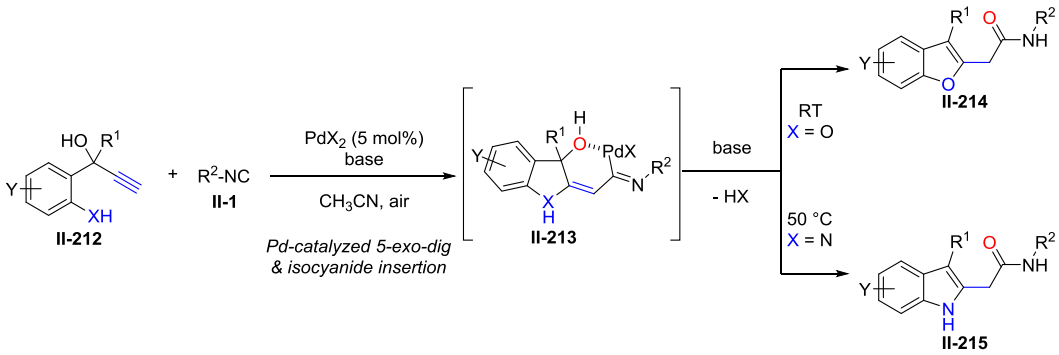
[179] B. Liu, Y. Li, M. Yin, W. Wu, H. Jiang, *Chem. Commun.* **2012**, *48*, 11446.
[180] Acidic proton : (a) Z.-Y. Gu, T.-H. Zhu, J.-J. Cao, X.-P. Xu, S.-Y. Wang, S.-J. Ji, *ACS Catal.* **2014**, *4*, 49; (b) Z. Chen, H.-Q. Duan, X. Jiang, Y.-M. Zhu, S.-J. Ji, S.-L. Yang, *J. Org. Chem.* **2015**, *80*, 8183; (c) H. Duan, Z. Chen, L. Han, Y. Feng, Y. Zhu, S. Yang, *Org. Biomol. Chem.* **2015**, *13*, 6782.; (d) G. C. Senadi, W.-P. Hu, S. S. K. Boominathan, J.-J. Wang, *Chem. – Eur. J.* **2015**, *21*, 998; (e) Y.-Y. Pan, Y.-N. Wu, Z.-Z. Chen, W.-J. Hao, G. Li, S.-J. Tu, B. Jiang, *J. Org. Chem.* **2015**, *80*, 5764.
[181] Csp^2–H (a) M. Tobisu, S. Imoto, S. Ito, N. Chatani, *J. Org. Chem.* **2010**, *75*, 4835; (b) J. Li, Y. He, S. Luo, J. Lei, J. Wang, Z. Xie, Q. Zhu, *J. Org. Chem.* **2015**, *80*, 2223; (c) U. K. Sharma, N. Sharma, J. Xu, G. Song, E. Van der Eycken, *Chem. Eur. J.* **2015**, *21*, 4908; (d) W. Kong, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2015**, *137*, 16028; (e) W. Kong, Q. Wang, J. Zhu, *Angew.Chem. Int. Ed.* **2016**, *55*, 9714; (f) Y.-J. Liu, H. Xu, W.-J. Kong, M. Shang, H.-X. Dai, J.-Q. Yu, *Nature* **2014**, *515*, 389; (g) S. Vidyacharan, A. Murugan, D. S. Sharada, *J. Org. Chem.* **2016**, *81*, 2837.
[182] Csp^3–H: T. Nanjo, C. Tsukano, Y. Takemoto, *Org. Lett.* **2012**, *14*, 4270.

isocyanide **II-1**, *o*-(alkynyl)aniline **II-209** and lithium halide. It has been suggested that the first step of this reaction was a trans-halopalladation of Pd-(II) species which afforded the intermediate **II-211** before isocyanide insertion (Scheme 156).[183]



Scheme 156: Pd-catalyzed isocyanide insertion via trans-halopalladation as initial step.

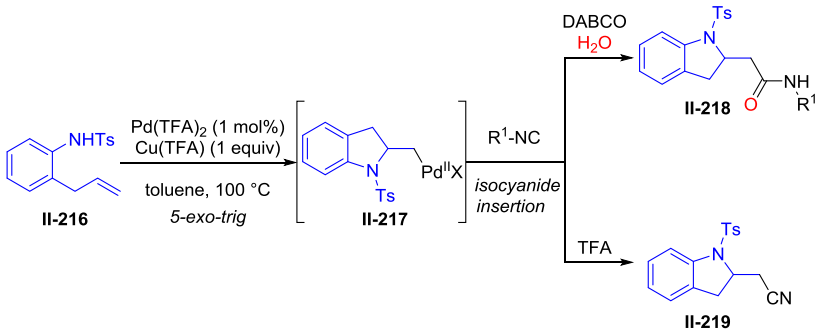
Later, Reddy illustrated the Pd-catalyzed domino process of isocyanide **II-1** and phenyl propargyl alcohol derivative **II-212**. In this reaction it was proposed that the first step was an via oxy/amino palladation (depending of the heteroatom X of compound **II-212**) in *anti* and 5-*exo-dig* fashion to produce intermediate **II-213**. After a reductive elimination/oxidative addition/protodepalladation sequence, the heterocycles **II-214** or **II-215** were isolated in moderate to good yields (Scheme 157)[184]



Scheme 157: Pd-catalyzed isocyanide insertion via 5-*exo-dig* cyclization as initial step.

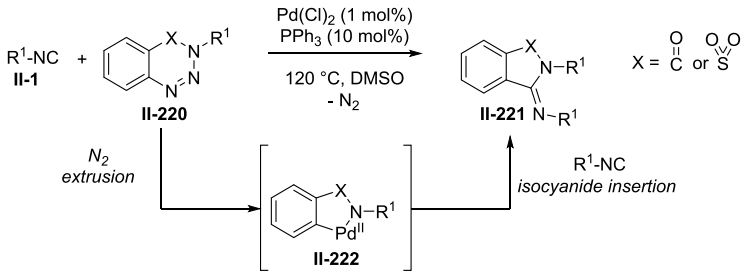
The palladium catalyzed *5-exo-trig* cyclization/isocyanide insertion reaction using *N*-sulfonyl-2-allylaniline and isocyanide has also been described by Jiang and Wu. Interestingly, the imidoyl palladium **II-217** resulting from the isocyanide insertion could be converted in amides **II-218** or cyanides **II-219** depending on the additive (Scheme 158)[185]

[183] B. Liu, H. Gao, Y. Yu, W. Wu, H. Jiang, *J. Org. Chem.* **2013**, *78*, 10319.
[184] N. Thirupathi, M. H. Babu, V. Dwiwedi, R. Kant, M. S. Reddy, *Org. Lett.* **2014**, *16*, 2908.
[185] H. Jiang, H. Gao, B. Liu, W. Wu, *Chem. Commun.* **2014**, *50*, 15348.



Scheme 158: Pd-catalyzed isocyanide insertion via 5-*exo-trig* cyclization as initial step.

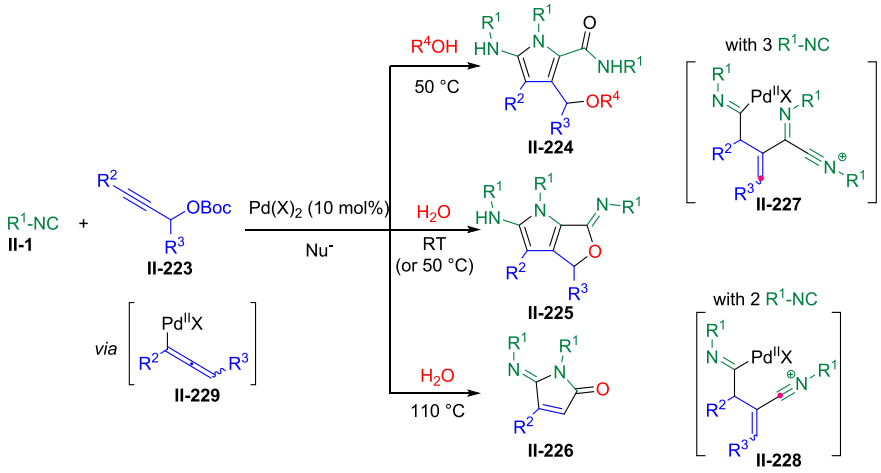
It is also possible to synthesize 3-(imino)isoindolin-1-ones **II-221** via palladium-catalyzed isocyanide insertion of isocyanide **I-1 and** triazine **II-220**. In this transformation the denitrogenation of the triazine **II-220** gave the 5-membered azapalladacycle **II-222** which delivered the desired heterocycle **II-221** after isocyanide insertion (Scheme 159). [186]



Scheme 159: Pd-catalyzed isocyanide insertion via N_2 extrusion as initial step.

More recently, our group and the group of Jiang reported almost simultaneously the palladium-catalyzed multicomponent reaction for the synthesis of pyrroles (**II-224 or II-225**) and iminopyrrolones (**II-226**). In this reaction, the first intermediate was the (σ-allenyl)palladium-(II) **II-229**. Incorporation of two or three isocyanide **II-1** was possible depending on the temperature (Scheme 160).[187]

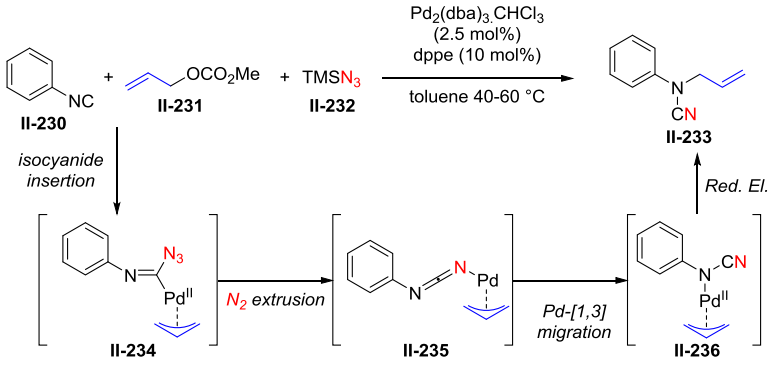
[186] T. Miura, Y. Nishida, M. Morimoto, M. Yamaguchi, M. Murakami, *Org. Lett.* **2011**, *13*, 1429.
[187] (a) J. Peng, Y. Gao, W. Hu, Y. Gao, M. Hu, W. Wu, Y. Ren, H. Jiang, *Org. Lett.* **2016**, *18*, 5924; (b) G. Qiu, Q. Wang, J. Zhu, *Org. Lett.* **2017**, *19* 270.



Scheme 160: Pd-catalyzed isocyanide insertion via (σ-allenyl)palladium-(II) species.

Ketenimine formation via Pd-catalyzed isocyanide insertion

In 2001, Yamamoto reported the unprecedented palladium catalyzed 3-CR of aryl isocyanide **II-230**, allyl carbonate **II-231** and $TMSN_3$ **II-232**. The proposed mechanism of this reaction started with the formation of the [π-(allyl)PdN_3] complex. After isocyanide insertion in the Pd-N_3 bond and Curtius type rearrangement, the carbodiimide intermediate **II-235** was formed. Final 1,3-palladium migration and reductive elimination produced the allyl cyanamides **II-233**. (Scheme 161).[188]

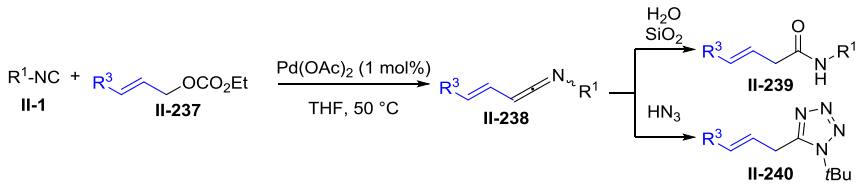


Scheme 161: Allyl cyanamide formation via Pd-carbodiimide intermediate

Inspired by the initial work of Yamamoto, our group described in 2016 the facile ketenimine **II-238** synthesis using isocyanide **II-1** and allyl carbonate **II-237** with palladium. This reaction was initiated by the formation of the π-allyl complex, which presumably adopted the η^1-allyl form. After isocyanide insertion into the Pd-allyl bond and β-hydride elimination, the α,β-unsaturated ketenimine **II-238** was obtained in good yield. This

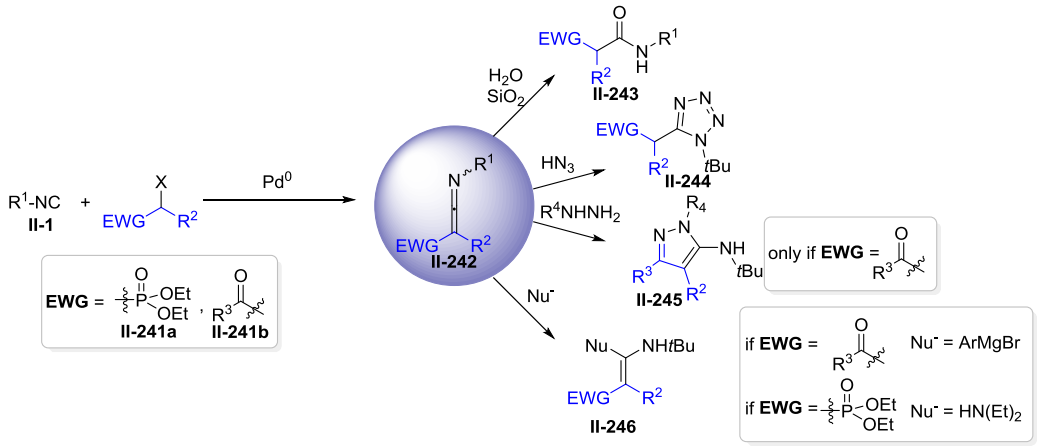
[188] S. Kamijo, T. Jin, Y. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 9453.

ketenimine **II-238** could quickly be converted in amides **II-239** or tetrazoles **II-240** depending of its further treatment (Scheme 162).[189a]



Scheme 162: Ketenimine formation via π-allyl complex.

It has also been illustrated that α-halo methylphosphonate **II-241a** and α-haloketones **II-241b** furnished α-EWG ketenimine **II-242** (Scheme 163). Further modifications of the ketenimine functionality afforded α-EWG amides **II-243**, tetrazoles **II-244**, 5-aminopyrazoles **II-245** or α-EWG enamines **II-246** .[189b,c]

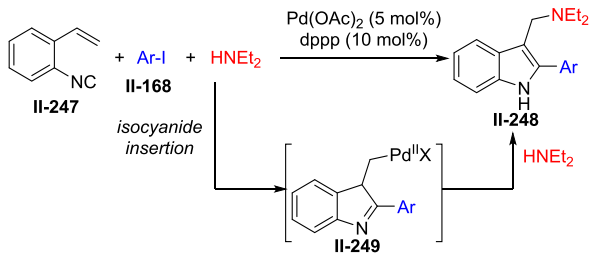


Scheme 163: Ketenimine formation via Pd-enolated intermediate.

Pd-catalyzed insertion of isocyanides bearing participating functional group

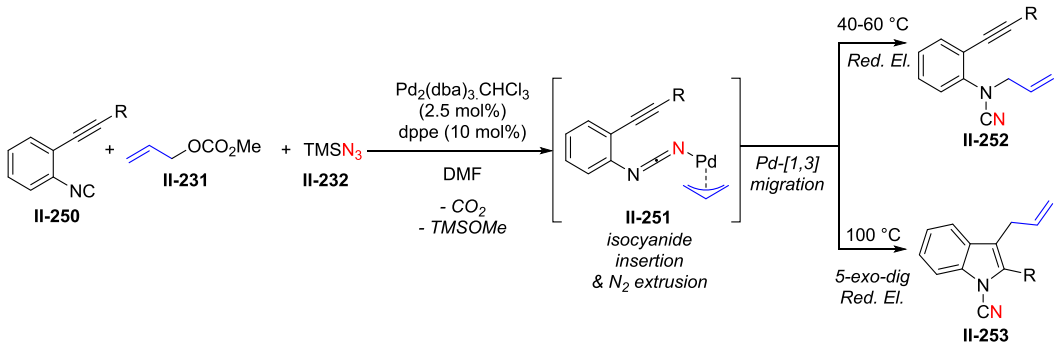
To explore the various possibilities of the palladium-catalyzed isocyanide insertion, modified isocyanides have also been used instead of the classical alkyl isocyanides. In 2002, Takahashi used *o*-alkenylphenyl isocyanide **II-247** with aryl iodide **II-168** and diethylamine for the synthesis of indoles derivative **II-248**. This Pd-catalyzed isocyanide insertion/*5-exo-trig*/reductive elimination sequence afforded the heterocycle **II-248** in moderate yields (40-60% yield) (Scheme 164).[190]

[189] (a) G. Qiu, M. Mamboury, Q. Wang, J. Zhu, *Angew.Chem. Int.Ed.* **2016**, *55* ,15377; (b) Q. Yang, C. Li, M.-X. Cheng, S.-D. Yang, *ACS Catal.* **2016**, *6*, 4715; (c) M. Mamboury Q. Wang, J. Zhu, *Chem. Eur. J.* **2017**, *23*, 12744.
[190] K. Onitsuka, S. Suzuki and S. Takahashi, *Tetrahedron Lett.* **2002**, *43*, 6197.



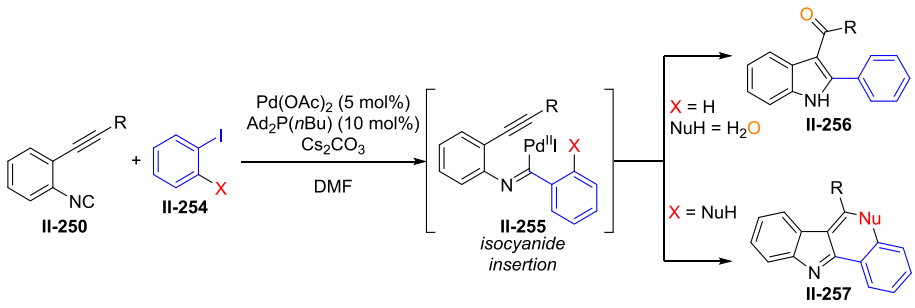
Scheme 164: Palladium-catalyzed isocyanide insertion of *o*-alkenylphenyl isocyanide, aryl iodide and a secondary amine.

o-Alkynyl isocyanobenzene can also be used as isocyanide partner. For example, Yamamoto described the divergent synthesis of allyl cyanamide **II-252** and *N*-cyanoindole **II-253** using the isocyanide **II-250** (Scheme 165).[191]



Scheme 165: Palladium catalyzed isocyanide insertion of *o*-Alkynyl isocyanobenzene, allyl carbonate and $TMSN_3$.

In 2013, *o*-alkynyl isocyanobenzene **II-250** has been used with aryl iodide **II-254** in a palladium-catalyzed isocyanide insertion. After formation of the imidoyl palladium intermediate **II-255**, incorporation of water afforded the 3-acyl-2-arylindole **II-256**. If a heteroatom was present in *ortho* of the aryl iodide, tetracyclic derivative **II-257** were formed in good yield. It is important to note that the isocyanide **II-250** was added dropwise to obtain decent yield of the products (Scheme 166). [192]



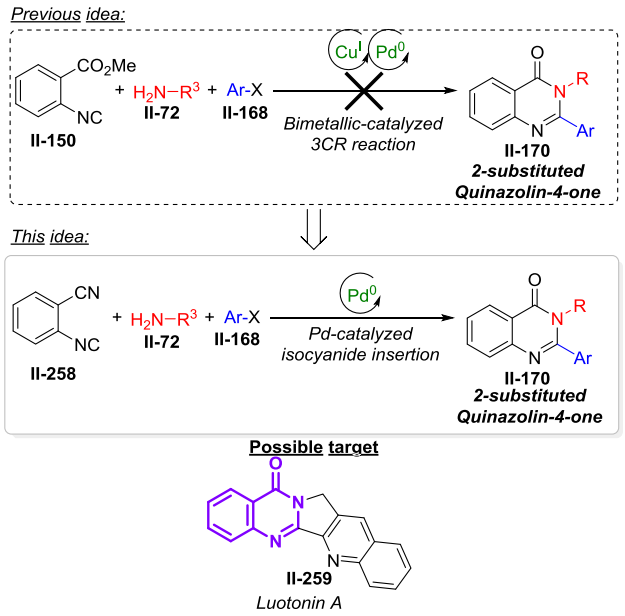
Scheme 166: Palladium catalyzed isocyanide insertion of *o*-alkynyl isocyanobenzene

[191] S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 11940.
[192] T. Nanjo, S. Yamamoto, C. Tsukano, Y. Takemoto, *Org. Lett.* **2013**, *15*, 3754.

Our idea

We reported previously in the Chapter 3 that the 3-CR reaction involving methyl *o*-isocyanobenzoate **II-150**, primary amine **II-72** and aryl iodide **II-168** in presence of copper/palladimum bimetallic system did not permit the formation of C-2 substituted quinazolin-4-ones **II-170**.

In order to perform the synthesis of this heterocycle **II-170**, we hoped to develop the palladium-catalyzed isocyanide insertion/lactamization sequence using *o*-isocyanobenzonitrle **II-258**, primary amine **II-72** and aryl halide **II-168**. This methodology could allow the formation of luotonin A **II-259**, a natural product found in the Chinese herbal medicinal plant *Paganum niggelastrum*, which possesses cytotoxic activity towards murine leukemia cell line (Scheme 167).[193]



Scheme 167: Proposed Pd-catalyzed 3-CR reaction for the synthesis of 2-substituted quinazolin-4-one.

Results & Discussion

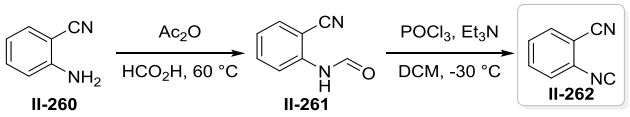
o-Isocyanobenzonitrile as starting material

In this approach we decided to use the more stable *o*-isocyanobenzonitrile **II-258** instead of methyl *o*-isocyanobenzoate **II-150**, which is known to polymerize when the reaction mixture is heated.

o-Isocyanobenzonitrile **II-258** has been described only once by Ito in 1999 in the isocyanide insertion/6π-electrocyclization reaction for the synthesis of 2,3-disubstituted

[193] A. Cagir, S. H. Jones, R. Gao, B. M. Eisenhauer, S. M. Hecht, *J. Am Chem. Soc.* **2003**, *125*, 13628.

quinolines (Scheme 102).[123] This starting material could be easily synthesized using the classic formylation/dehydration sequence of *o*-cyanoaniline **II-260** (Scheme 168).



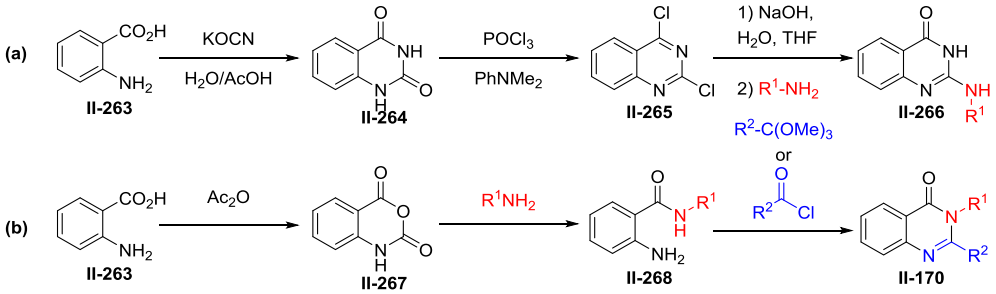
Scheme 168: *o*-Isocyanobenzonitrile synthesis.

Background on 2-substituted quinazolin-4-one synthesis

Quinazolinone is a motif found in several bioactive compounds. Possessing anti-bacterial, antifungal, antiviral and enzyme inhibitor properties, this potent heterocycle has been extensively studied.[194] Synthetically, many different strategies have been designed for the 2-substituted quinazolin-4-ones **II-170** formation. [195]

Anthranilic acid **II-263** has been used as starting material for the synthesis of C-2 quinazolin-4-ones **II-266**. After formation of the quinazoline-2,4(1H,3H)-dione **II-264** with potassium cyanate, double dehydration offered the 2,4-dichloroquinazoline **II-265**. Treatment with water in basic conditions followed by addition of primary amine give the desired aminated heterocycle **II-266** (Scheme 169, **(a)**). [196]

C-2 substituted quinazolin-4-ones **II-170** could be made from anthranilic acid **II-263** via the formation of the cyclic carbamic anhydride **II-267**. Addition of amine followed by acyl chloride or orthoester afford the desired quinazolin-4-one **II-170** (Scheme 169, **(b)**).



Scheme 169: Quinazolinones synthesis from anthranilic acid.

[194] (a) S. Sinha, M. Srivastava, *Prog. Drug Res.* **1994**, *43*, 143; (b) S. E. de Laszlo, C. S. Quagliato, W. J. Greenlee, A. A. Patchett, R. S. L. Chang, V. J. Lotti, T.-B. Chen, S. A. Scheck, K. A. Faust, S. S. Kivlighn, T. S. Schorn, G. J. Zingaro, P. K. S. Siegl, *J. Med. Chem.* **1993**, *36*, 3207; (c) N. J. Liverton, D. J. Armstrong, D. A. Claremon, D. C. Remy, J. J. Baldwin, R. J. Lynch, G. Zhang, R. J. Gould, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 483; (d) W. Zhang, J. P. Mayer, S. E. Hall, J. A. Weigel, *J. Comb. Chem.* **2001**, *3*, 255.

[195] Review on Quinazolinone synthesis: (a) J. Bergman, A. Witt, *Curr. Org. Chem.* **2003**, *7*, 659. (b) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893.(c) D. J. Connolly, D. Cusack, T. P. O'Sullivan, P. J. Guiry, *Tetrahedron* **2005**, *61*, 10153. (d) A. Patil, O. Patil, B. Patil, J. Surana, *Mini-Rev. Med. Chem.* **2011**, *11*, 633.

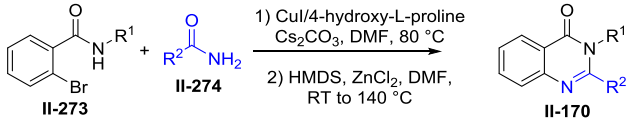
[196] J. DeRuiter, A. N. Brubaker, J. Millen, T. N. Riley, *J. Med.Chem.* **1986**, *29*, 627.

La Rosa and coworkers described the synthesis of C-2 substituted quinazolin-4-one **II-271** via [4+2] cycloaddition/[2+2] cycloaddition/ring expansion sequence from the uncommon dienophile **II-269** and phenylisocyanate **II-270** (Scheme 170).

[197]

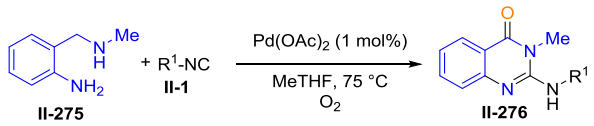
Scheme 170: Diels-Alder type reaction for the quinazolin-4-ones synthesis.

It was also possible to synthesize C-2 substituted quinazolin-4-one **II-170** via copper catalyzed-amidation of *o*-bromo benzamide **II-273** with primary amide **II-274** (Scheme 171). [198]



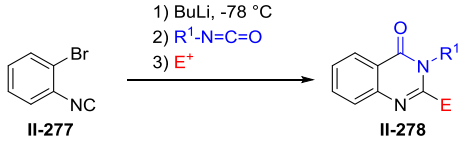
Scheme 171: Copper catalyzed-aryl amidation for quinazolin-4-ones synthesis.

Palladium-catalyzed isocyanide insertion of isocyanide **II-1** and *N*-methyl *o*-(amino)benzylamine **II-275** gave C-2 aminated quinazolin-4-one **II-276**. In this reaction, a further benzylic oxidation occured under oxygen atmosphere (Scheme 172). [176b]



Scheme 172: Pd-catalyzed isocyanide insertion for the C-2 aminated quinazolin-4-ones synthesis.

The lithiation of *o*-bromobenzoisonitrile **II-277** gave the heterocycle **II-278** in moderate to good yield after reactions with alkyl isocyanate and an electrophile (Scheme 173). [199]

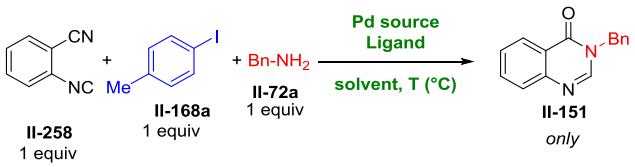


Scheme 173: ortho lithiation from *o*-bromobenzoisonitrile for C-2 substituted quinazolin-4-one synthesis.

[197] P. D. Croce, R. Ferracioli, C. La Rosa, *Heterocycles* **1997**, *45*, 1309.
[198] L. Xu, Y. Jiang, D. Ma, *Org. Lett.* **2012**, *14*, 1150.
[199] A. V. Lygin, A. de Meijere, *Org. Lett.* **2009**, *11*, 389.

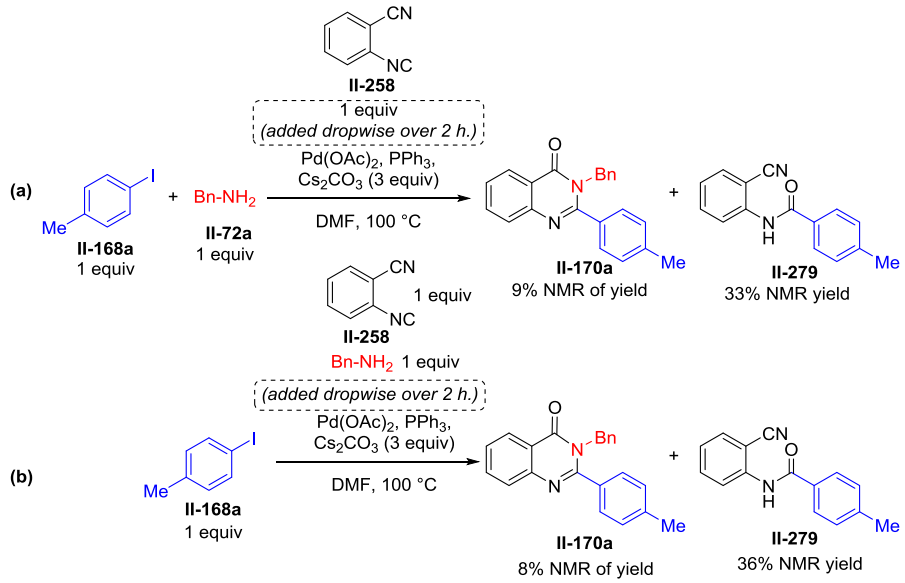
Condition optimization

In order to develop another method to synthetize 2-substituted quinazolin-4-one **II-170**, we started our investigation with *o*-isocyanobenzonitrile **II-258**, *p*-idodotoluene **II-168a** and benzyl amine **II-72a** as starting materials. All the reactions were set up in the glovebox and all the reagents were mixed together before heating. Unfortunately, after the screening of palladium sources, ligands, solvents and temperatures, only the C-2 unsubstituted quinazolin-4-one **II-151** was obtained (Scheme 174). With these conditions, the imidoyl palladium intermediate was not formed.



Scheme 174: Preliminary screening for the Pd-catalyzed 3-CR.

Inspired by the work of Takemoto (Scheme 166),[192] we tried to add the isocyanide **II-258** dropwise in the reaction mixture. In this case, the incorporation of the aryl iodide **II-168a** was possible and the desired product **II-170a** was formed in 9% yield accompanied with the amide **II-279** in 33% yield (Scheme 175, **(a)**). Benzyl amine and isocyanide were also added dropwise simultaneously but similar results were observed (Scheme 175, **(b)**).

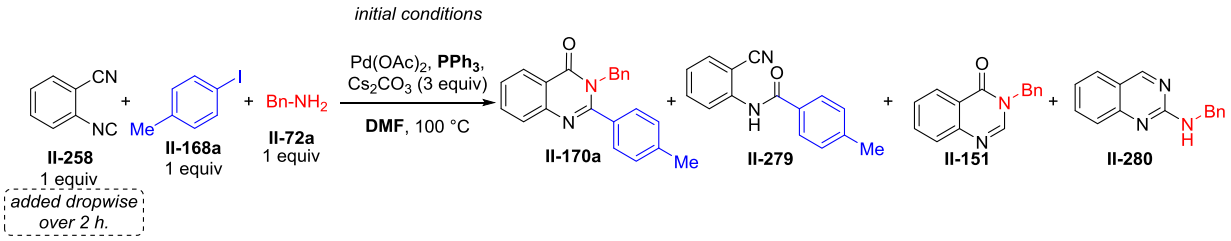


Scheme 175: Pd-catalyzed 3-CR with dropwise addition of isocyanide.

As the latter encouraging result suggested the succesfull formation of the imidoyl palladium intermediate, different parameters were modified (Table 23). 2 equivalents of benzyl amine gave 25% yield of **II-170a** and 31% of **II-279** (Entry 2). Toluene as solvent or $P(Ad)_2Bu$ as ligand were not promising for this reaction (Entries 3 and 4). An excess of

benzyl amine furnished the mixture of undesired product **II-151** and **II-280** in 19% and 39% yield respectively (Entry 5).

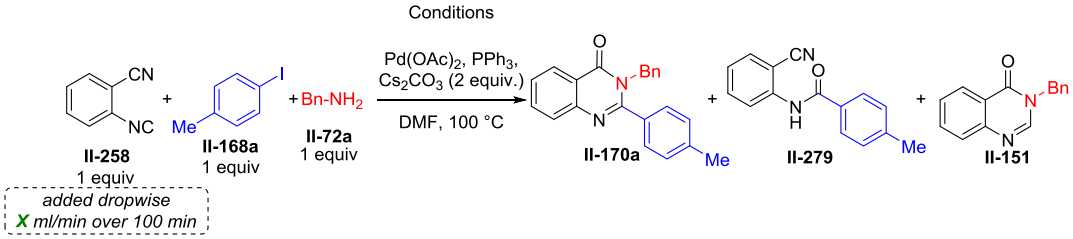
Table 23: Initial screening.



Entry	Modification of the *initial condition*	NMR yield
1*	-	9% of **II-170a** + 33% of **II-279**
2	2 equiv of Bn-NH_2	25% of **II-170a** + 31% of **II-279**
3	2 equiv of Bn-NH_2 + Toluene instead of DMF	20% of **II-170a**
4	2 equiv of Bn-NH_2 + Pd(Ad)$_2$Bu instead of P(Ph)$_3$	14% of **II-170a** + 37% of **II-279**
5	10 equiv of Bn-NH_2	19% of **II-151** + 39% of **II-280**

The addition rate of isocyanide was examined (Table 24). Addition of the isocyanide in only 20 min gave a mixture of **II-170a**, **II-279** and **II-151** in poor yield (Entry 4). Slower additions (0.01, 0.02 & 0.05 mL/min) gave better results and an addition rate of 0.02 mL.min^{-1} was chosen (Entries 1 to 3).

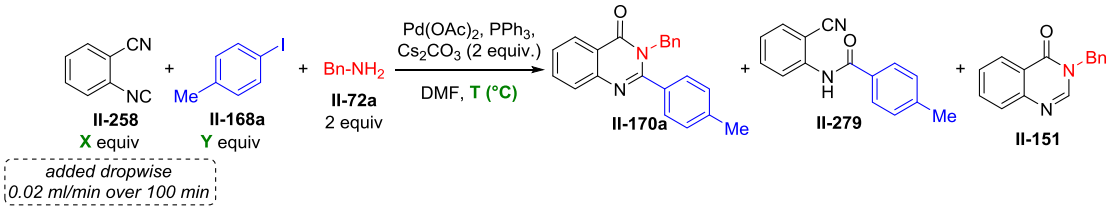
Table 24: Addition rate of the isocyanide adding screening.



Entry	Flow of the adding	NMR yield
1	0.01ml/min (addition of 2mL over 200 min)	23% yield of **II-170a** + 24% yield **II-279** + 5% yield of **II-151**
2	**0.02ml/min** (addition of 2mL over 100 min)	24% yield of **II-170a** + 34% yield of **II-279**
3	0.05ml/min (addition of 2mL over 40 min)	21% yield of **II-170a** + 31% yield of **II-279**
4	0.1ml/min (addition of 2mL over 20 min)	15% yield of **II-170a** + 18% yield of **II-279** + 15% yield of **II-151**

By varying the equivalents of isocyanide and *p*-iodotoluene **II-168a** (Table 25, entry 1 to 4), we observed that 1.5 equivalent of isocyanide with 1 equivalent of *p*-iodotoluene and 2 equivalents of amine gave the best hit with 57% NMR yield of products resulting from the imidoyl palladium intermediate (**II-170a** & **II-279**). The temperature had an important impact on the formation of **II-170** (entries 5 to 7). Indeed, when the temperature was fixed to 80 °C, the desired 2-substituted quinazolin-2one **II-170a** was produced in 48% NMR yield.

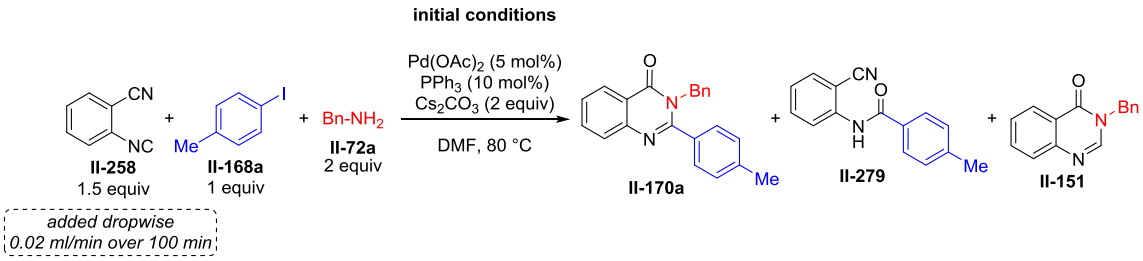
Table 25: Equivalent and temperature screening.



Entry	T (°C)	Equivalent (X, Y)	NMR yield
1*	100 °C	(X = 1, X = 1)	24% yield of **II-170a** + 34% of **II-279**
2	100 °C	(X = 1, Y = 1.5)	17% yield of **II-170a** + 21% of **II-279**
3	100 °C	(X = 1.5, Y = 1)	27% yield **II-170a** + 37% yield of **II-279** + 32% yield of **II-151**
4	100 °C	(X = 2, Y = 1)	30% yield **II-170a** + 27% yield **II-279** + 40% yield **II-151**
5	**80 °C**	(X = 1.5, Y = 1)	48% yield of **II-170a** +31% yield of **II-279**
6	120 °C	(X = 1.5, Y = 1)	31% yield of **II-170a** + 34% yield of **II-279**
7	60 °C	(X = 1.5, Y = 1)	21% yield of **II-170a** + 44% of **II-151**

Starting from this so far best reaction conditions (Entry 1), different other parameters were screened (Table 26). The use of 3Å molecular sieves avoided the formation of the amide **II-279** but **II-170a** was obtained in 25% yield only (Entry 2). 2 mol% of $Pd(OAc)_2$ with 4 mol% of PPh_3 furnished only the quinazolin-4one **II-151** (Entry 3). The ligand $P(Ad)_2Bu$ instead of PPh_3 furnished low yield of the desired **II-170a** (Entry 4). 3 equivalents of Cs_2CO_3 or heating to 100 °C did not favor the reaction (Entries 5 and 6). Increasing the loading of $Pd(OAc)_2$ and PPh_3 (10 and 20 mol% respectively) gave a complex mixture of **II-170a**, **II-279** and **II-151**.

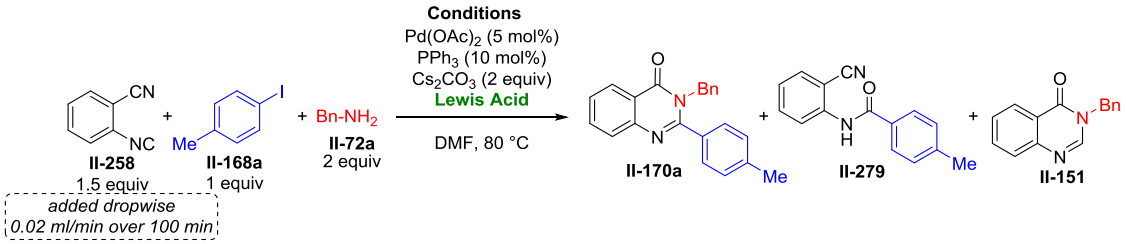
Table 26: Further screening.



Entry	Modification of the condition	NMR yield
1*	-	48% yield of **II-170a** +31% yield of **II-279**
2	**3Å MS**	25% yield of **II-170a** + 28% yield of **II-151**
3	$Pd(OAc)_2$ (**2** mol%), PPh_3 (**4** mol%)	40% yield of **II-151**
4	**$P(Ad)_2Bu$** instead of PPh_3	13% yield of **II-170a** + 44% yield of **II-151**
5	Cs_2CO_3 (**3** equiv)	27% yield of **II-170a** + 24% yield of **II-151**
6	**100 °C**, **3 Å MS**, Cs_2CO_3 (**3** equiv)	20% yield of **II-170a** + 11% yield of **II-151**
7	**100 °C**, $Pd(OAc)_2$ (**10** mol%), PPh_3 (**20** mol%)	29% yield of **II-170a** + 11% yield of **II-279** + 38% yield of **II-151**

Several Lewis acids were added as additives in order to activate the cyanide for the final cyclization. Regrettably, the degradation of the starting materials was observed when 1 or 0.2 equivalent of different Lewis acids were used (Table 27).

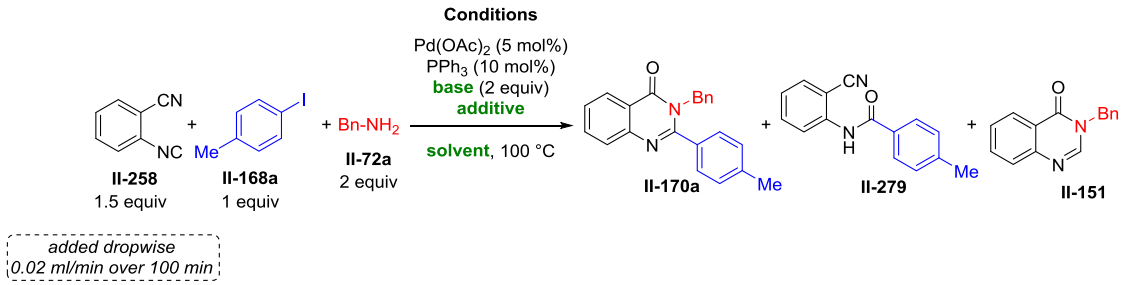
Table 27: Lewis acid screening



Entry	Lewis acid	NMR yield
1*	$CuCl_2$ (1 equiv)	Degradation
2	CuI (1 equiv)	Degradation
3	$BF_3.Et_2O$ (1 equiv)	Degradation
4	$AlCl_3$ (1 equiv)	Degradation
5	$AlCl_3$ (20 mol%)	Degradation
6	CuI (20 mol%)	Degradation
7	$FeCl_3$ (20 mol%)	Degradation
8	$ZnCl_2$ (20 mol%)	degradation
9	$InCl_3$ (20 mol%)	degradation
10	$SnCl_4$ (20 mol%)	degradation

Other bases and solvents were screened (Table 28). Degradation of the starting material was observed in toluene (Entry 1 & 2). With DMF or dioxane as solvent, CsOPiv and the combination of Cs_2CO_3 and pivalic acid lead to unfruitful results (Entry 3 to 6). Without base, the product **II-151** was formed in 21% yield (Entry 7). The use of other aromatic solvents such as *p*-xylene or mesytelene afforded **II-170a** in only 11% and 16% yield respectively (Entries 8 and 9).

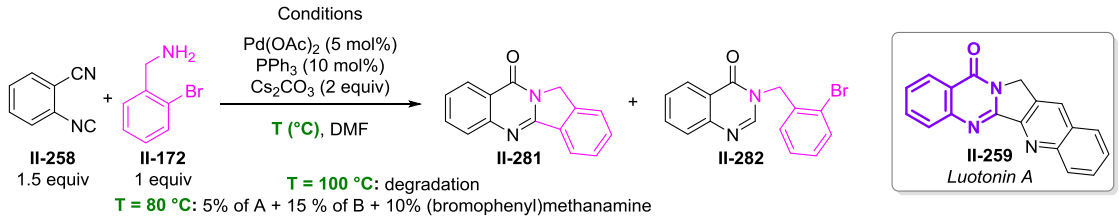
Table 28: Base/solvent screening.



Entry	solvent	Condition	NMR yield
1	toluene	CsOPiv (2 equiv)	Degradation
2	toluene	Cs_2CO_3 (2 equiv), PivOH (0.3 equiv)	Degradation

3	dioxane	CsOPiv (2 equiv)	14% of **II-170a** + 5% of **II-151**
4	dioxane	Cs_2CO_3 (2 equiv), PivOH (0.3 equiv)	6% of **II-170a** + 14% of **II-151**
5	DMF	CsOPiv (2 equiv)	15% of **II-279**
6	DMF	Cs_2CO_3 (2 equiv), PivOH (0.3 equiv)	15% of **II-151**
7	DMF	No base	21% yield **II-151**
8	p-xylene	-	Messy, 11% of **II-170a**
9	mesytelene	-	Messy, 16% of **II-170a**

Before putting this project in stand-by because of the lack of results, we finally quickly focused on the synthesis of a scaffold close to Luotonin A (Scheme 176). At 100 °C with 5 mol% of $Pd(OAc)_2$, 10 mol% PPh_3 and 2 equivalents of Cs_2CO_3, *o*-isocyanobenzonitrile **II-258** and *o*-bromobenzylamine **II-172** furnished a complex reaction mixture. Decreasing the temperature to 80 °C, gave only traces amount of the product **II-281** and 15% NMR yield of the C-2 unsubstituted quinazolin-2-one **II-282**.



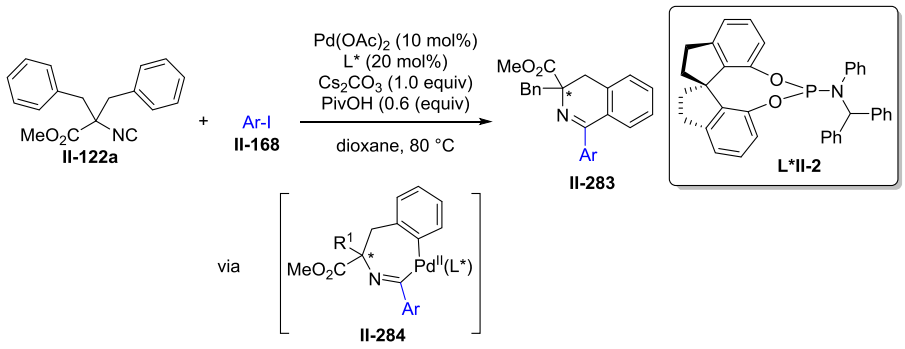
Scheme 176: Pd-catalyzed isocyanide insertion with *o*-bromo benzylamine.

The best result obtained during the investigation on the Pd-catalyzed 3-CR of *o*-isocyanobenzonitrile, benzyl amine and *p*-iodotoluene, was obtained with 5 mol% of $Pd(OAc)_2$, 10 mol% of PPh_3, 2 equiv of Cs_2CO_3 in DMF at 80 °C and afforded the 2-arylated quinazolin-4-one **II-170a** in 48% yield. This project was put on hold to explore another Pd-catalyzed transformation involving isocyanide insertion.

Alternative idea: Pd-catalyzed isocyanide insertion/C(sp^3)-H activation sequence with cyclopropanes.

At the beginning of this year, Zhu and coworkers developed the enantioselective desymmetrization of α,α-dibenzylisocyanoacetate **II-122a**. In this transformation, the isocyanide insertion furnished the imidoyl palladium intermediate, followed by an enantioselective C(sp^2)-H activation. The resulting 7-membered palladacycle **II-284** underwent reductive elimination to deliver the enantioenriched 3,4-dihydroisoquinolines **II-283**. The ligand SPINOL-derived phosphoramidite **L*II-2** was important to reach high enantioselectivies (Scheme 177).[200]

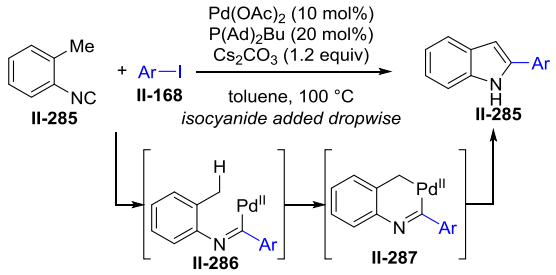
[200] J. Wang, D.-W. Gao, J. Huang, S. Tang, Z. Xiong, H. Hu, S.-L. You, Q. Zhu *ACS Cat.* **2017**, *7*, 3832.



Scheme 177: Desymmetrization of α,α-dibenzyl isocyanoacetate via Pd-catalyzed isocyanide insertion/C-H activation

C(sp^3)-H activation is an important method to introduce complexity in molecules. The incorporation of the palladium in unactivated C(sp^3)-H bond has been particularly studied. Generally, an appropriate directing group is needed to favor the selective C-H activation of the transition metal.[201]

In 2012, Takemoto *et al.* reported the first Pd-catalyzed isocyanide insertion/C-H activation sequence for the synthesis of C-2 arylated indoles derivatives **II-285**. In this transformation, they have also shown that the slow addition of isocyanide is important to obtain good yields (Scheme 178).[182]



Scheme 178: Pd-catalyzed isocyanide insertion/C(sp^3)-H activation of *o*-isocyanotoluene

The cyclopropane ring is commonly present in potent molecules. Due to the strain of this small ring, which gives a slight acidity to the proton, the C(sp^3)-H bond of the 3-membered ring can be functionalized. Recent reports of cyclopropane (Csp^3)-H activation found enantioselective applications for the synthesis of interesting building blocks.[202]

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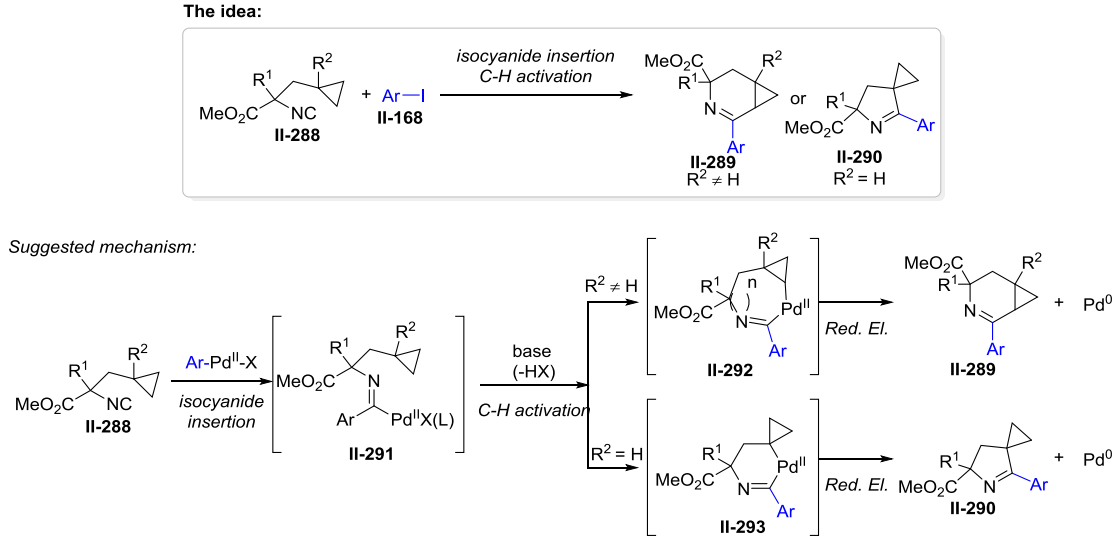
[201] For reviews on C(sp^3)-H activation, see: (a) O. Baudoin, *Chem. Soc. Rev.* **2011** , *40*, 4902. (b) H. Li, B.-J. Li, Z.-J. Shi, *Catal. Sci.Technol.* **2011**, *1*, 191. (c) L. McMurray, F. O'Hara, M. J. Gaunt, *J. Chem. Soc. Rev.* **2011**, *40*, 1885. (d) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976. (e) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; (f) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654; (f) N. Dastbaravardeh, M. Christakakou, M. Haider, N. Schnürch *Synthesis* **2014**, *46*, 1421.

[202] Chapter on C-H activation of cyclopropane: D. S. Roman, A. B. Charette *Top. Organomet. Chem.* **2016**, *56*, 91 and ref cited in; (a) J. Pedroni, N. Cramer, *Angew. Chem. Int. Ed.* **2015**, *54*, 11826; (b) J. Pedroni, T. Saget, P. A. Donets, N. Cramer, *Chem. Sci.* **2015**, *6*, 5164.

By taking advantage of the cyclopropane and the isocyanide reactivities, we proposed to develop a Pd-catalyzed isocyanide insertion/C(sp^3)-H activation reaction of methyl 2-isobutyl 3-cyclopropyl-2-isocyanopropanoate **II-288**. In this transformation, we suggested that the formation of the imidoyl palladium **II-291** could then follow two different pathways depending on the nature of R^2. If $R^2 \neq H$, the 7-membered pallacycle **II-292** could give the azabicyclo[4.1.0]hept-2-ene **II-289** after reductive elimination. In the case of $R^2 = H$, the 6-membered palladacycle **II-293** could be formed and should afford the C-2 arylated azaspiro[2.4]hept-4-ene **II-290** (Scheme 179).

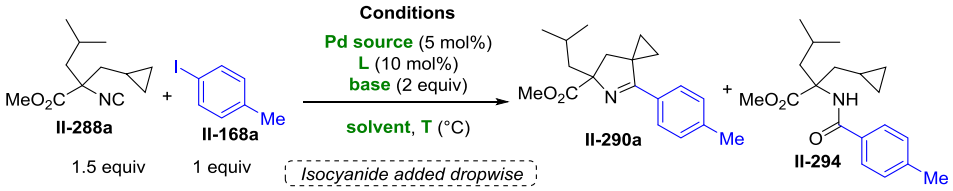


Scheme 179: Pd-catalyzed isocyanide insertion/ C-H activation of methyl 2-substituted 3-cyclopropyl-2-isocyanopropanoate.

Methyl 2-isobutyl 3-cyclopropyl-2-isocyanopropanoate as starting material

The investigation on this transformation was performed with methyl 2-substituted 3-cyclopropyl-2-isocyanopropanoate **II-288a** and *p*-iodotoluene **II-168a** as starting material (Table 29). When Cs_2CO_3 was used as base in toluene, only degradation was observed regardless of the palladium source and the ligand used (Entry 1 to 3). If DMF was used with Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%), the amide **II-294** was produced in 50% NMR yield (Entry 4). Interestingly, by replacing the base with CsOPiv, 20% NMR yield of the desired spiro compound **II-290a** was obtained (Entry 5). Heating to 110 °C gave **II-290a** in 30% NMR yield (Entry 7). Note that the combination Cs_2CO_3 and PivOH gave only 17% NMR yield of the azaspiro[2.4]hept-4-ene **II-290a** (Entry 6).

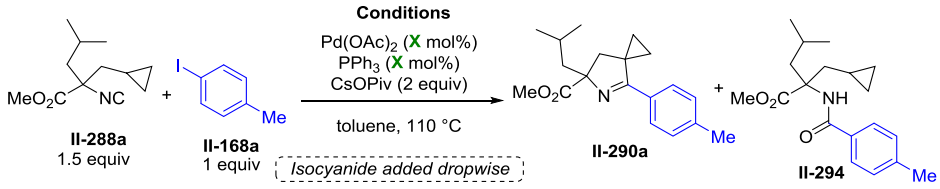
Table 29: Preliminary screening



Entry	Pd /Ligand (5 mol%/10 mol%)	base	solvent	T (°C)	NMR yield
1	$Pd(OAc)_2/PPh_3$	Cs_2CO_3 (2 equiv)	toluene	100 °C	Slight degradation
2	$Pd(OAc)_2/P(Ad)_2Bu$	Cs_2CO_3 (2 equiv)	toluene	100 °C	Slight degradation
3	$PdCl_2/PPh_3$	Cs_2CO_3 (2 equiv)	toluene	100 °C	Slight degradation
4	$Pd(OAc)_2/PPh_3$	Cs_2CO_3 (2 equiv)	DMF	90 °C	50% of **II-294**
5	$Pd(OAc)_2/PPh_3$	CsOPiv (1.2 equiv)	toluene	90 °C	20% of **II-290a**
6	$Pd(OAc)_2/PPh_3$	Cs_2CO_3 (1.5 equiv), PivOH (0.3 equiv)	toluene	110 °C	17% of **II-290a**
7	$Pd(OAc)_2/PPh_3$	CsOPiv (1.5 equiv)	toluene	110 °C	30% of **II-290a**

The catalyst loading was also optimized (Table 30). By decreasing the amount of palladium and ligand (2 mol% and 4 mol% respectively), no reaction was observed (Entry 3). Lower yield of **II-290a** was obtained when 10 mol% of palladium acetate and 20 mol% of triphenylphosine were used (Entry 2). Finally, the starting materials were recovered when the the reaction mixture was diluted or when the isocyanide was added in one portion (Entry 4 & 5).

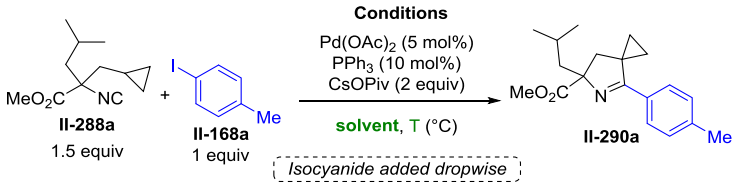
Table 30: Catalyst loading/dropwise addition



Entry	Catalyst loading	Modification	NMR yield
1*	5mol%/10 mol%	-	30% of **II-290a**
2	10mol%/20 mol%	-	12% of **II-290a**
3	2mol%/4 mol%	-	No reaction (starting material recovered)
4	5mol%/10 mol%	Conc. [**0.025M**]	No reaction (starting material recovered)
5	5mol%/10 mol%	***One portion of isocyanide***	No reaction (starting material recovered)

The screening of the solvents was then explored. Toluene (110 °C), dioxane (90 °C) or mesitylene (130 °C) gave similar yield of the spiro compound **II-290a**. The best result was obtained with *p*-xylene at 130 °C and gave the desired product in 42% yield **II-290a**.

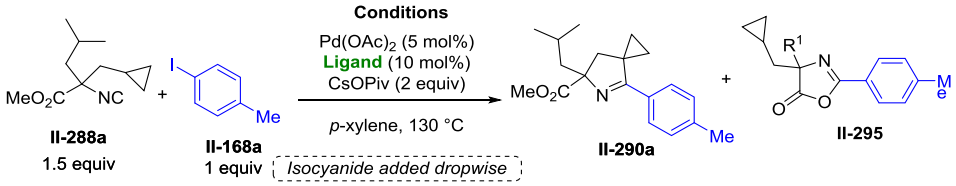
Table 31: solvent screening



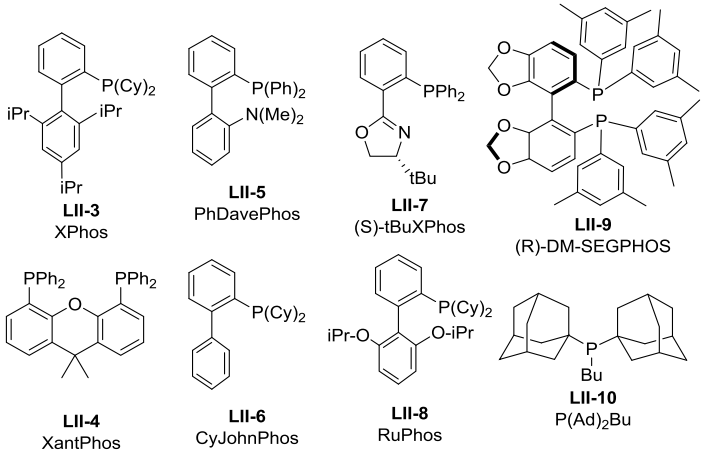
Entry	solvent	T (°C)	NMR yield
1*	toluene	110 °C	30% of **II-290a**
2	dioxane	90 °C	33% of **II-290a**
3	*p*-xylene	130 °C	42% of **II-290a**
4	*p*-xylene	120 °C	33% of **II-290a**
5	mesitylene	130 °C	34% of **II-290a**

Cesium pivalate as base and *p*-xylene as solvent lead to a significant yield of 42% of the desired product. To further increased the yield of **II-290a**, different ligands were studied (Table 32). Monodentate phosphine such as XPhos, CyJohnPhos and RuPhos gave a complex reaction mixture (Entries 2, 5 and 7) whereas Xantphos and SEGPHOS were not suitable ligand for this reaction (Entries 2 and 8). PhDavephos and $P(Ad)_2nBu$ permited to form **II-290a** albeit in low yield (24-25%, Entries 4 and 9). It is notable that *t*BuPhox favoured the formation of the unexpected azlactone **II-295** in 24% yield (Entry 6).

Table 32: Ligand screening.

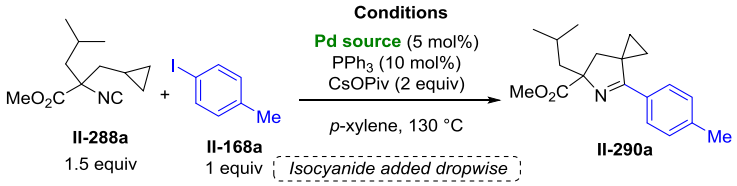


Entry	Ligand	NMR yield
1*	PPh_3	42% of **II-290a**
2	XPhos	Degradation of the starting material
3	XantPhos	Degradation of the starting material
4	PhDavePhos	25% of **II-290a**
5	CyJohnPhos	Degradation of the starting material
6	*t*BuPhox	24% of a new product **II-295**
7	RuPhos	Degradation of the starting material
8	(R)-DM-SEGPhos	Messy
9	$P(Ad)_2nBu$	24% of **II-290a**



Different sources of palladium were also tried (Table 33). Palladium tetrakis and $P(Cy)_3.HBF_4$ gave a complex reaction mixture (Entry 3 and 4). NHC palladium complex lead to **II-290a** in only 15% NMR yield (Entry 5). Palladium halide complexes were also screened and interestingly $PdCl_2$ afford the azaspiro[2.4]hept-4-ene **II-290a** in 44% yield (Entry 2). However, by changing the chloride to bromide ($PdBr_2$), **II-290a** was formed in 12% yield only.

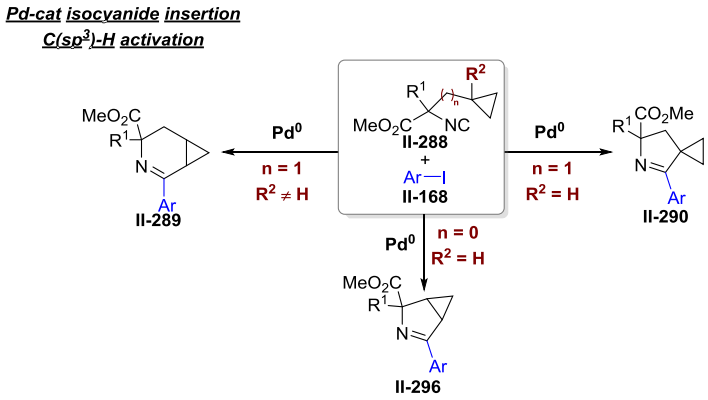
Table 33: Palladium source screening.



Entry	Palladium source	NMR yield
1*	$Pd(OAc)_2$	42% of **II-290a**
2	$PdCl_2$	44% of **II-290a**
3	$Pd(Ph_3)_4$	Degradation of the starting material
4	$P(Cy)_3.HBF_4$	Slight degradation, starting material only
5	PEPPSI-IPr catalyst	15% of **II-290a**
6	$Pd(Br)_2$	22% of **II-290a**
7	$Pd(TFA)_2$	39% of **II-290a**
8	$Pd(dba)_2$	35% of **II-290a**

The azaspiro[2.4]hept-4-ene derivative **II-290a** has been synthesized in 44% yield when methyl 2-isocbutyl 3-cyclopropyl-2-isocyanopropanoate and *p*-iodotoluene reacted in the presence of $PdCl_2$ (5 mol%), PPh_3 (10 mol%) and CsOPiv (2 equiv) in *p*-xylene at 130 °C. With this promising result, further optimizations are currently ongoing.

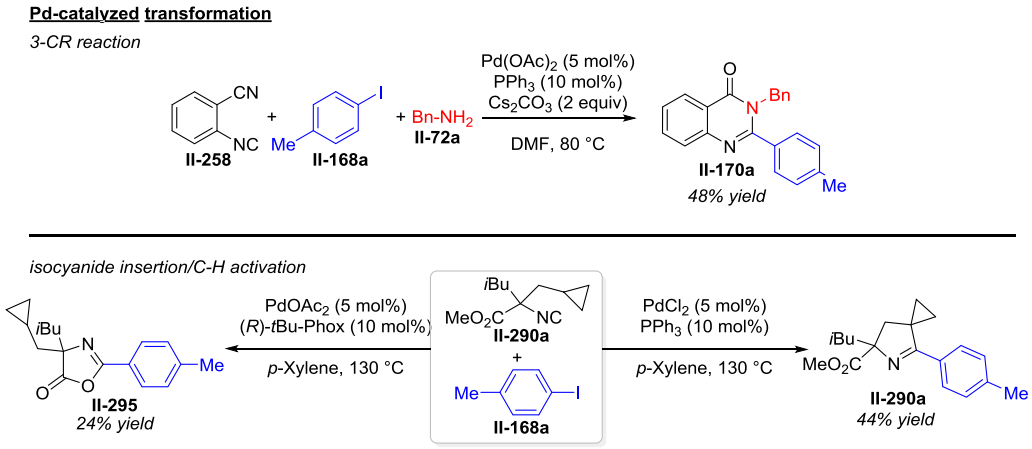
By modifying the isocyanoacetate starting material **II-288**, other nitrated heterocycles (**II-289**, **II-290** or **II-296**) might be synthesized via the similar Pd-catalyzed isocyanide insertion/C(sp^3)-H activation sequence. These different scaffolds could be potent bioactive compound used in medicinal chemistry (Scheme 180).



Scheme 180: Other potential scaffold via the Pd-catalyzed isocyanide insertion/C(sp^3)-H activation isocyanoacetate.

Conclusion

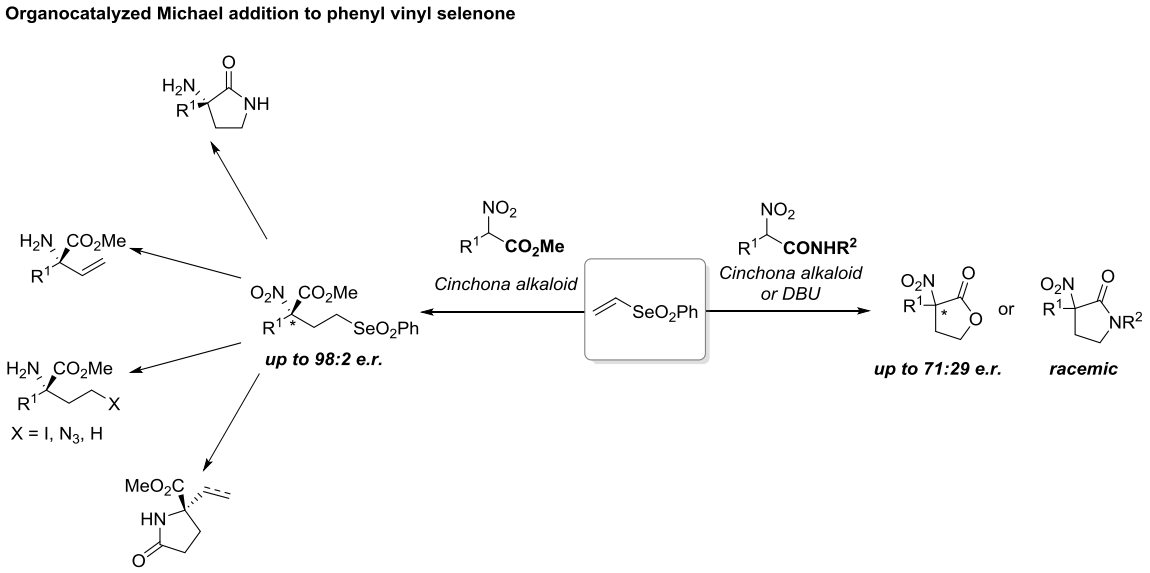
Palladium-catalyzed reactions involving isocyanide bearing participating functional group have been investigated. On one hand, the three component reaction of *o*-isocyanobenzonitrile **II-258**, *p*-iodotoluene **II-168a** and benzyl amine **II-72a** in the presence of a catalytic amount of $Pd(OAc)_2$, PPh_3 and 2 equivalents of Cs_2CO_3 afforded the 2-substituted quinazolin-4-one **II-170a** in moderate yield (Scheme 181). On the other hand, the palladium-catalyzed isocyanide insertion/C(sp^3)-H activation of methyl 2-isobutyl 3-cyclopropyl-2-isocyanopropanoate **II-295** and *p*-iodotoluene **II-168a** in the presence of a catalytic amount of $PdCl_2$ and triphenylphosphine in xylene at 130 °C deliver the C-2 arylated azaspiro[2.4]hept-4-ene **II-290a** in 44% yield. We also noticed that changing the ligand to *t*BuPhox leads to the azlactone **II-295** in 24% yield. In these two projects, a further optimization of the reaction condition would be necessary to reach higher yield of these different important heterocycles.



Scheme 181: Palladium catalyzed reaction involving *o*-isocyanobenzonitrle and 2-substituted 3-cyclopropyl-2-isocyanopropanoate

General Conclusion

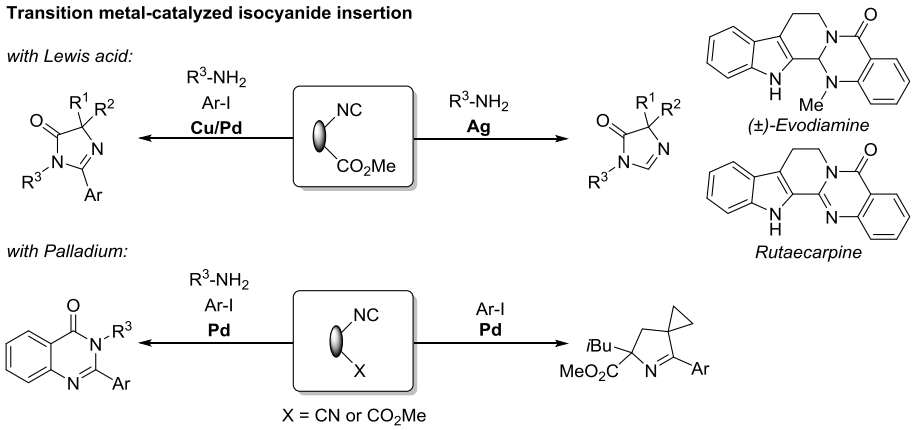
During this PhD, we have initially focused our effort on the development of enantioselective organocatalytic conjugate addition of different Michael donors to phenyl vinyl selenone. As initial acceptor, α-substituted nitroacetate have been used in this reaction. In the presence of *Cinchona* alkaloid derivative as organocatalyst, the formation of α,α-dialkyl α-nitroacetates has been accomplished in excellent yield and good enantioselectivity. The resulting Michael adducts have been converted to linear and cyclic quaternary α–amino acids by taking advantage of their rich functionalities. α-Substituted nitroamides were subsequently used as nucleophiles with phenyl selenone. In the presence of *Cinchona* alkaloid, the organocatalytic Michael addition/intramolecular S_N2/hydrolysis sequence afforded γ-lactone in good yield and moderate enantioselectivity. The formation of racemic γ-lactam has also been reported following a similar sequence when DBU was used as base (Scheme 182).



Scheme 182: Organocatalyzed Michael addition to phenyl vinyl selenone.

In the second part of this PhD, we have concentrated our attention on the design of transition metal-catalyzed insertions of isocyanides bearing participating functional group for the synthesis of heterocycles and natural products. On the one hand, the silver-catalyzed isocyanide insertion of α,α-disubstituted isocyanoacetate with primary amine furnished 3,5,5-trisubstituted imidazolones in good to excellent yield. This methodology has been applied on methyl *o*-isocyanobenzoate for the synthesis of two natural products, evodiamine and rutaecarpine. Then, a copper/palladium-catalyzed 3-CR reaction of α,α-disubstituted isocyanoacetate, primary amide and aryl iodide have been developed to afford 2,3,5,5-tetrasubstituted imidazolones in moderate to good yield. On the other hand, palladium-

catalyzed isocyanide insertion has been explored. The Pd-catalyzed 3-CR of *o*-isocyanobenzonitrile, aryl iodide and primary amine produced 2-substituted quinazolin-4-one in moderate yield. We have also investigated the Pd-catalyzed isocyanide insertion/C(sp^3)-H activation of methyl 2-isobutyl 3-cyclopropyl-2-isocyanopropanoate with aryl iodide which delivered C-2 arylated azaspiro[2.4]hept-4-ene in moderate yield (Scheme 183).



Scheme 183: Transition metal-catalyzed isocyanide insertion of unusual isocyanide.

Part III: Experimental data

General information

Reagents and solvents were purchased from commercial sources (Aldrich, Acros, Merck, Fluka and VWR international) and preserved under argon. More sensitive compounds were stored in a desiccator or glove-box if required. Reagents were used without further purification unless otherwise noted.

All reactions were performed under argon (or nitrogen) unless otherwise noted. When needed, glassware was dried overnight in an oven (T > 100 °C) or under vacuum with a heat gun (T > 200 °C).

When solvents are indicated as dry they were either purchased as such, distilled prior to use or were dried by a passage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc., based on the Grubb's design.[1]

Reactions heated by microwave irradiation are performed in a CEM Discover SP microwave instrument.

Flash column chromatography was performed using Silicycle P60 silica: 230-400 mesh (40-63 µm) silica.

Reactions were monitored using Merck Kieselgel 60F254 aluminium or glass backed plates. TLC's were visualized by UV fluorescence (254 nm) then stained with one of the following TLC stains: $KMnO_4$, phosphomolybdic acid, ninhydrin, pancaldi, *p*-anisaldehyde, vanillin.

NMR spectra were recorded on a Brüker AvanceIII-400, Brüker Avance-400 or Brüker DPX-400 spectrometer at room temperature, ^{1}H frequency is at 400.13 MHz, ^{13}C frequency is at 100.62 MHz. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 MHz for proton and 0.1 MHz for carbon (ref: $CHCl_3$ [^{1}H: 7.26 ppm, ^{13}C: 77.2 ppm] , MeOH [^{1}H: 3.31 ppm, ^{13}C 49.0 ppm], DMSO [^{1}H: 2.50 ppm, ^{13}C 39.5 ppm]). Coupling constants (J) were reported in Hz to the nearest 0.1 Hz. Peak multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad).

IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacleTM ATR accessory as neat films compressed onto a Zinc Selenide window. The spectra are reported in cm^{-1}. Abbreviations used are: w (weak), m (medium), s (strong) and br (broad).

Mass spectra were obtained with a Waters ACQUITY H-class UPLC/MS ACQ- SQD by electron ionisation (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI +). The accurate masses were measured by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters.

Enantiomeric ratios were determined with a Thar SFC Investigator system using chiral stationary phase.

Optical rotations α_D were obtained with a Jasco P-2000 polarimeter (589 nm).

Melting points were determined using a Stuart SMP30.

When a rigorously inert and dry atmosphere was needed reactions were carried out in a PureLab HE 4GB 2500 Glove-box System from Innovative Technologies inc.

Part I

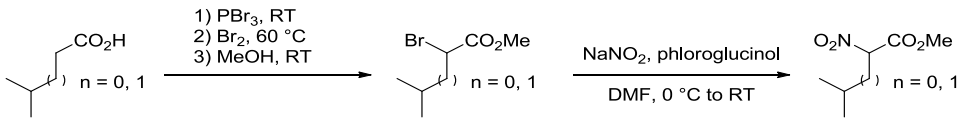
Chapter 1

For all general procedures the order of addition of reagents has to be respected.

Phenyl vinyl selenone (**2a**)[203], alkyl α-alkyl nitroacetates **4a-4e**, [204] **4g**,[205] **4h-4k**,[206] **4l**,[207] **4m-4o**,[208] *Cinchona* alkaloid-based organocatalysts **QN-2**, **QN-3**, **QD-3**, **QN-5**, **QN-8**, **QN-9**, **QN-10**, **QN-11**, **QN-12** **β-iCD** and **epiQN-3** were synthesized according to the literature procedures.[209]

General procedures

General procedure A:



Preparation of α-alkyl α-bromoacetate:

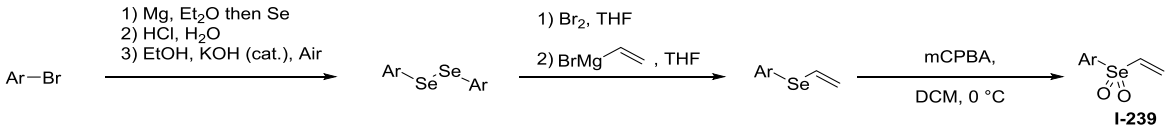
To the carboxylic acid (1 equiv) was added dropwise PBr_3 (1.1 equiv) at room temperature during 0.5 hour. To the resulting mixture was added dropwise Br_2 (1.1 equiv) during 0.5 hour (HBr gas was trapped with an exit tubing which was connected to a saturated aqueous solution of $NaHCO_3$) and the reaction mixture was heated to 60 °C for 2 additional hours. The reaction mixture was cooled to room temperature and MeOH was added dropwise over 1h. The reaction mixture was then concentrated under reduced pressure to give the α-bromoacetate which was used in the next reaction without further purification.

Preparation of α-alkyl α-nitroacetate: [205]

To a solution of α-bromoacetate (1 equiv) and phloroglucinol (1.2 equiv) in DMF (0.2 M) at 0 °C was added $NaNO_2$ (1.5 equiv). The reaction mixture was slowly warmed to room temperature and stirred until complete consumption of the starting material (TLC monitoring, around 1 hour). The reaction mixture was diluted with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product **4f**.

General procedure B:

Synthesis of aryl vinyl selenone:[210],[211],[212]



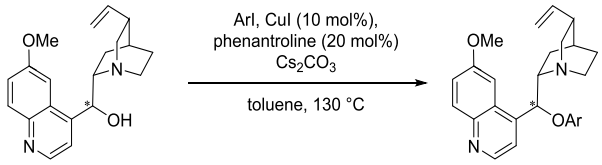
To a suspension of magnesium (729 mg, 30.0 mmol, 1 equiv) in Et_2O (60 mL, 0.5 M) was added dropwise aryl bromide (30.0 mmol, 1 equiv) at such a rate that the reflux was maintained during 1 hour. Selenium metal (2.37 g, 30.0 mmol, 1 equiv) was then added portionwise (4-5 portions, caution: the reaction is exothermic). The reaction mixture was vigorously stirred at 40 °C for 2 hours. The reaction mixture was cooled to 0 °C and

diluted slowly with cold water. Concentrated HCl (20 mL) was added slowly and the reaction mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was diluted with ethanol (50 mL) and a flow of O_2 gas was bubbled to the reaction mixture during 12 hours. The reaction mixture was concentrated and the crude product was filtered through silica gel to afford the diaryl diselenide.

To a solution of the diaryl diselenide (1 equiv) in THF (0.1 M) was added and vinyl magnesium bromide (2.2 equiv) at 0 °C. The reaction mixture was warmed to room temperature and stirred during 4 hours. The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to (pure PE as eluent) afford the pure product.

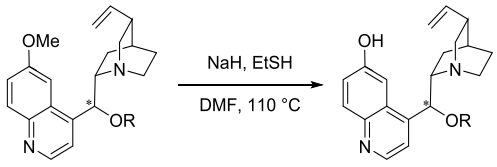
To a solution of the aryl vinyl selenide (1 equiv) in DCM (0.1 M) at 0 °C was added portionwise mCPBA (4 equiv) during 10 min. The reaction mixture was warmed to room temperature and stirred until complete consumption of the starting material (TLC monitoring, around 2 hours). The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the desired aryl vinyl selenone **2**.

General procedure C:[213]



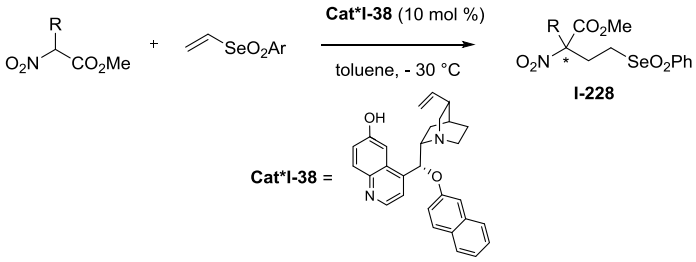
To a suspension of quinine (1.5 equiv), CuI (10 mol%), phenanthroline (20 mol%) and Cs_2CO_3 (1.2 equiv) in dry toluene (0.2 M) was added aryl iodide (1 equiv). The resulting mixture was heated to 60 °C and stirred for 12 hours. The reaction mixture was cooled to room temperature, diluted with a saturated aqueous solution of $NaHCO_3$ and extracted with AcOEt (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

General procedure D: [214]



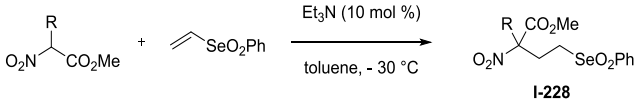
To a solution of NaH (1.5 equiv) in dry DMF (0.1 M) at 0 °C was added dropwise EtSH (1.5 equiv) during 10 min. To the reaction mixture was added a solution of *Cinchona* alkaloid derivative (1 equiv) in dry DMF (0.1) and the resulting mixture was quickly heated to 110 °C. The reaction mixture was stirred until complete consumption of the starting material (TLC monitoring, around 5 hours). The reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

General procedure E:



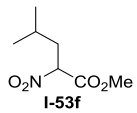
To a solution of aryl vinyl selenone **2** (0.05 mmol, 1 equiv) and **QN-7** (0.005 mmol, 0.1 equiv) in toluene (0.1 mL) at - 30 °C was added α-substituted nitroacetate **4** (0.06 mmol, 1.2 equiv)**.** The reaction mixture was stirred at - 30 °C until complete consumption of the starting material (TLC monitoring, around 48 hours). The reaction mixture was warmed to room temperature and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

General procedure F: Synthesis of (±)-5



To a solution of phenyl vinyl selenone (**2a**) (0.05 mmol, 1 equiv) and α-substituted nitroacetate **4** (0.06 mmol, 1.2 equiv) in toluene (0.5 mL) was added Et_3N (0.06, 1.2 equiv). The reaction mixture was stirred until complete consumption of the starting material (TLC monitoring, around 12 hours) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Characterization data



I-53f

Procedure A:

Yield: 155 mg, 32% (2 steps) Eluent: AcOEt/PE, 0:100 to 85:15

Aspect: colorless oil

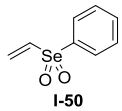
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 5.20 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.83 (s, 3H), 2.28 (ddd, *J* = 14.3, 10.0, 5.6 Hz, 1H), 1.94 (ddd, *J* = 14.3, 8.6, 5.1 Hz, 1H), 1.70 – 1.58 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 165.5, 86.8, 53.7, 39.0, 25.2, 22.6, 21.5.

IR: 2961 (w), 1755 (s), 1561 (s), 1373 (w), 1272 (w), 1207 (w).

HRMS: (ESI) calcd for $C_7H_{12}NO_4$ [M+H] 174.0766; found 174.0779.

Aryl vinyl selenones



I-50

Procedure B:

Yield: 8.03 g, 91% from the corresponding diselenide, Eluent: AcOEt/PE, 80:20 to 90:10

Aspect: white solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.00 – 7.92 (m, 2H), 7.74 – 7.68 (m, 1H), 7.67 – 7.61 (m, 2H), 6.99 (dd, *J* = 16.6, 9.1 Hz, 1H), 6.72 (dd, *J* = 16.6, 2.0 Hz, 1H), 6.45 (dd, *J* = 9.1, 2.0 Hz, 1H).

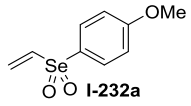
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 141.3, 139.0, 134.5, 131.3, 130.5, 127.1.

^{77}Se NMR (76.31 MHz, $Se(Me)_2$): δ 966.8

IR: 3043 (w), 1448 (w), 1370 (w), 1221 (w), 1064 (w), 980 (m), 929 (s), 880 (s), 761 (s), 685 (m).

HRMS: (ESI) calcd for $C_8H_8NaO_2Se^+$ $[M+Na]^+$ 238.9582; found 238.9591.

Melting point: 109.5-111.5 °C



I-232a

Procedure B:

Yield: 130 mg, 20% (over 3 steps) Eluent: AcOEt/PE, 70:30 to 90:10

Aspect: white solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.96 – 7.77 (m, 2H), 7.12 – 7.06 (m, 2H), 6.97 (dd, *J* = 16.5, 9.1 Hz, 1H), 6.67 (dd, *J* = 16.5, 1.9 Hz, 1H), 6.40 (dd, *J* = 9.1, 1.9 Hz, 1H), 3.89 (s, 3H).

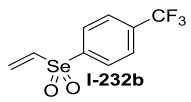
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 164.4, 139.4, 132.0, 130.6, 129.2, 115.7, 56.0.

^{77}Se NMR (76.31 MHz, $Se(Me)_2$): δ 966.1

IR: 3040 (w), 2902 (w), 1587 (m), 1575 (w), 1494 (m), 1259 (s), 1073 (m), 926 (s), 876 (s), 830 (s).

HRMS: (ESI) calcd for $C_9H_{11}O_3Se^+$ $[M+H]^+$ 246.9868; found 246.9873.

Melting point: 112.5-114.5 °C



I-232b

Procedure B:

Yield: 1.60 g, 28% (over 3 steps) Eluent: AcOEt/PE, 70:30 to 90:10

Aspect: white solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.9 Hz, 2H), 7.91 (d, *J* = 7.9 Hz, 2H), 7.02 (dd, *J* = 16.4, 9.0 Hz, 1H), 6.80 (dd, *J* = 16.4, 2.1 Hz, 1H), 6.52 (dd, *J* = 9.0, 2.1 Hz, 1H).

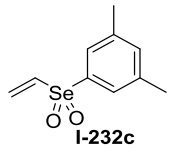
^{13}C NMR (100.62 MHz, $CDCl_3$) δ 144.9, 138.6, 136.3 (q, *J* = 32.3 Hz), 132.4, 127.9, 127.6 (q, *J* = 3.8 Hz), 123.0 (q, *J* = 272.7 Hz).

^{77}Se NMR (76.31 MHz, $Se(Me)_2$): δ 946.7

IR: 2922 (w), 1601 (m), 1398 (w), 1320 (s), 1164 (m), 1119 (s), 1072 (s), 1011 (s), 824 (s).

HRMS: (ESI) calcd for $C_9F_3H_8O_2Se^+$ $[M+H]^+$ 284.9636; found 284.9642.

Melting Point: 101-103 °C



I-232c

Procedure B:

Yield: 715 mg, 16% (over 3 steps), Eluent: AcOEt/PE, 70:30 to 90:10

Aspect: white solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.56 – 7.55 (m, 2H), 7.31 – 7.30 (m, 1H), 6.97 (dd, *J* = 16.5, 9.1 Hz, 1H), 6.71 (dd, *J* = 16.5, 1.9 Hz, 1H), 6.42 (dd, *J* = 9.1, 1.9 Hz, 1H), 2.42 (s, 6H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 140.9, 140.8, 139.2, 136.2, 131.0, 124.4, 21.5.

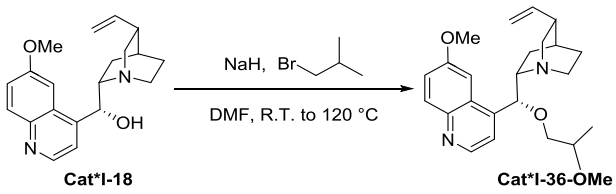
^{77}Se NMR (76.31 MHz, $Se(Me)_2$): δ 968.0

IR: 3091 (w), 3044 (w), 2337 (w), 1718 (w), 1458 (w), 1362 (w), 1008 (m), 929 (s), 882 (s), 850 (m), 677 (m).

HRMS: (ESI) calcd for $C_{10}H_{13}O_2Se^+$ $[M+H]^+$ 245.0075; found 245.0080.

Melting point: 161-163 °C

Catalysts



Cat*I-18 **Cat*I-36-OMe**

Procedure: To a solution of quinine (1 equiv) and NaH (5 equiv) in DMF previously stirred at room temperature for 2 hours, was added 1-bromo-2-methylpropane (5 equiv). The resulting mixture was heated to 120 °C for 12 hours. The reaction mixture was cooled to room temperature, diluted with water and extracted with AcOEt (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 21%, Eluent: AcOEt/NH_3, 99:1 to AcOEt/NH_3/MeOH, 97:1:2

Aspect: brown pale foam

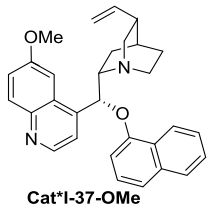
^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.5 Hz, 1H), 7.96 (d, *J* = 9.3 Hz, 1H), 7.36 (d, *J* = 4.5 Hz, 1H), 7.33 – 7.26 (m, 2H), 5.62 (ddd, *J* = 17.6, 10.3, 7.6 Hz, 1H), 5.22 – 5.12 (m, 1H), 4.93 – 4.78 (m, 2H), 3.89 (s, 3H), 3.55 – 3.40 (m, 1H), 3.18 – 2.97 (m, 4H), 2.78 – 2.67 (m, 1H), 2.67 – 2.56 (m, 1H), 2.34 – 2.21 (m, 1H), 1.90 – 1.71 (m, 4H), 1.57 – 1.38 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$) δ 157.9, 147.5, 144.6, 144.6, 141.3, 136.5, 131.8, 127.3, 121.9, 118.6, 114.7, 101.2, 80.4, 76.2, 60.1, 56.8, 56.0, 43.3, 39.6, 28.9, 27.8, 27.3, 21.4, 19.6, 19.5.

IR: 2925 (m), 2870 (w), 1735 (w), 1677 (w), 1621 (m), 1508 (m), 1364 (w), 1240 (s), 1107 (s), 1029 (s), 914 (m), 856 (s), 821 (m), 718 (m).

HRMS: (ESI) calcd for $C_{24}H_{33}N_2O_2^+$ $[M+H]^+$ 381.2537; found 381.2545.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$ = - 74 (*c* 0.3, $CHCl_3$)



Cat*I-37-OMe

Procedure C:

Yield: 73%, Eluent: AcOEt/NH_3, 99:1 to AcOEt/NH_3/MeOH, 98:1:1)

Aspect: brown pale foam

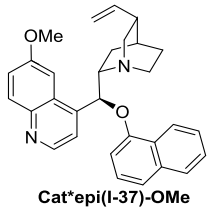
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.60 (d, *J* = 4.5 Hz, 1H), 8.58 – 8.54 (m, 1H), 8.11 – 8.05 (m, 1H), 7.85 – 7.80 (m, 1H), 7.63 – 7.58 (m, 1H), 7.58 – 7.51 (m, 1H), 7.48 – 7.39 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.09 (t, *J* = 8.1 Hz, 1H), 6.43 (d, *J* = 7.7 Hz, 1H), 6.23 (d, *J* = 2.9 Hz, 1H), 5.79 (ddd, *J* = 17.0, 10.3, 7.7 Hz, 1H), 5.06 – 4.90 (m, 2H), 4.01 (s, 3H), 3.54 – 3.43 (m, 1H), 3.42 – 3.34 (m, 1H), 3.22 – 3.12 (m, 1H), 2.82 – 2.67 (m, 2H), 2.39 – 2.30 (m, 1H), 2.30 – 2.20 (m, 1H), 2.04 – 1.94 (m, 2H), 1.82 – 1.72 (m, 1H), 1.68 – 1.57 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 158.3, 152.3, 147.9, 144.8, 143.7, 142.1, 134.8, 132.3, 128.0, 126.6, 126.6, 126.6, 125.9, 125.7, 122.0, 121.7, 120.8, 118.2, 114.6, 106.6, 100.9, 78.9, 60.6, 57.6, 56.0, 43.6, 40.3, 28.3, 28.3, 22.0.

IR: 3064 (w), 2937 (w), 2864 (w), 1621 (m), 1578 (m), 1508 (m), 1398 (m), 1265 (s), 1239 (s), 1102 (m), 914 (w), 792 (m), 771 (s), 733 (m).

HRMS: (ESI) calcd for $C_{30}H_{31}N_2O_2^+$ $[M+H]^+$ 451.2380; found 451.2395.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$ = + 249 (*c* 1.0, $CHCl_3$)



Cat*epi(I-37)-OMe

Procedure C:

Yield: 64%, Eluent: AcOEt/NH_3, 99:1 to AcOEt/NH_3/MeOH, 98:1:1

Aspect: brown pale foam

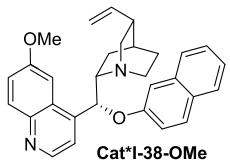
^{1}H NMR (400.13 MHz, $CDCl_3$): 8.68 (d, *J* = 4.5 Hz, 1H), 8.56 (d, *J* = 8.2 Hz, 1H), 8.05 (d, *J* = 9.3 Hz, 1H), 7.78 – 7.71 (m, 1H), 7.64 (d, *J* = 2.8 Hz, 1H), 7.57 – 7.45 (m, 3H), 7.40 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 5.93 (d, *J* = 7.5 Hz, 1H), 5.85 (ddd, *J* = 17.4, 10.4, 7.3 Hz, 1H), 5.08 – 4.94 (m, 2H), 4.01 (s, 3H), 3.78 – 3.64 (m, 1H), 3.61 – 3.46 (m, 1H), 3.26 (dd, *J* = 13.9, 10.0 Hz, 1H), 2.99 – 2.77 (m, 2H), 2.41 – 2.27 (m, 1H), 1.85 – 1.73 (m, 2H), 1.70 – 1.53 (m, 2H), 1.40 – 1.28 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 158.1, 153.4, 147.8, 144.9, 142.8, 141.7, 134.7, 132.3, 127.7, 127.5, 126.6, 126.1, 125.6, 125.6, 122.5, 121.6, 121.0, 120.5, 114.7, 106.9, 101.6, 78.2, 60.7, 56.7, 55.8, 42.6, 39.7, 28.1, 27.9, 24.8.

IR: 3062 (w), 2937 (w), 2864 (w), 1621 (m), 1578 (m), 1508 (s), 1265 (s), 1239 (s), 1097 (m), 913 (m), 854 (m), 772 (s), 732 (m).

HRMS: (ESI) calcd for $C_{30}H_{31}N_2O_2^+$ $[M+H]^+$ 451.2380; found 451.2384.

$[\alpha]_D^{26}$ = - 195 (*c* 1.0, $CHCl_3$)



Cat*I-38-OMe

Procedure C:

Yield: 63%, Eluent: AcOEt/NH_3, 99:1 to AcOEt/NH_3/MeOH, 98:1:1

Aspect: brown pale foam

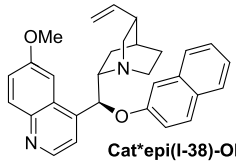
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.66 (d, *J* = 4.5 Hz, 1H), 8.09 (d, *J* = 10.0 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.49 – 7.42 (m, 4H), 7.35 – 7.27 (m, 2H), 7.21 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 6.18 – 6.12 (m, 1H), 5.76 (ddd, *J* = 17.0, 10.3, 7.6 Hz, 1H), 5.05 – 4.89 (m, 2H), 4.03 (s, 3H), 3.49 – 3.40 (m, 1H), 3.36 – 3.29 (m, 1H), 3.18 (dd, *J* = 13.7, 10.2 Hz, 1H), 2.81 – 2.68 (m, 2H), 2.38 – 2.31 (m, 1H), 2.12 – 2.05 (m, 1H), 2.01 – 1.95 (m, 1H), 1.94 – 1.90 (m, 1H), 1.67 – 1.57 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 158.4, 154.9, 147.8, 144.8, 143.6, 141.7, 134.4, 132.3, 129.8, 129.3, 127.7, 127.0, 126.6, 126.5, 124.1, 122.1, 118.6, 118.6, 114.7, 109.2, 101.0, 79.1, 60.4, 57.4, 56.1, 43.6, 40.0, 28.2, 27.8, 21.5.

IR: 2938 (w), 1621 (m), 1600 (w), 1509 (s), 1467 (m), 1255 (s), 1216 (s), 1178 (s), 1029 (w), 911 (m), 837 (m), 733 (s).

HRMS: (ESI) calcd for $C_{30}H_{31}N_2O_2^+$ $[M+H]^+$ 451.2380; found 451.2379.

$[\alpha]_D^{26}$ = + 216 (*c* 1.1, $CHCl_3$)



Cat*epi(I-38)-OMe

Procedure C:

Yield: 47%, Eluent: AcOEt/NH_3, 99:1 to AcOEt/NH_3/MeOH, 98:1:1

Aspect: brown pale foam

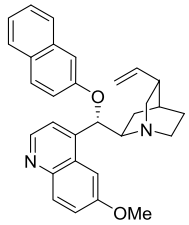
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.72 (d, *J* = 4.5 Hz, 1H), 8.04 (d, *J* = 9.3 Hz, 1H), 7.75 (d, *J* = 2.7 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.53 (d, *J* = 4.5 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.32 – 7.27 (m, 1H), 7.25 – 7.21 (m, 2H), 7.02 (d, *J* = 2.5 Hz, 1H), 5.86 – 5.73 (m, 2H), 5.08 – 4.91 (m, 2H), 4.03 (s, 3H), 3.70 – 3.56 (m, 1H), 3.43 – 3.36 (m, 1H), 3.36 – 3.29 (m, 1H), 2.94 – 2.86 (m, 1H), 2.86 – 2.79 (m, 1H), 2.37 – 2.25 (m, 1H), 1.76 – 1.67 (m, 2H), 1.66 – 1.56 (m, 1H), 1.47 – 1.34 (m, 1H), 1.18 – 1.07 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 158.1, 155.5, 147.6, 144.9, 142.7, 141.6, 134.1, 132.2, 129.4, 129.2, 127.6, 127.6, 126.8, 126.3, 123.9, 121.7, 121.2, 119.5, 114.6, 109.7, 101.8, 78.6, 60.3, 56.3, 55.8, 41.9, 39.7, 28.2, 27.7, 25.0.

IR: 2939 (w), 2864 (w), 1621 (m), 1509 (m), 1254 (m), 1215 (s), 1033 (m), 909 (m), 836 (m), 730 (s).

HRMS: (ESI) calcd for $C_{30}H_{31}N_2O_2^+$ $[M+H]^+$ 451.2380; found 451.2374.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = - 1 (*c* 1.1, $CHCl_3$)



Cat*I-39-OMe

Procedure C:

Y**ield:** 68%, Eluent: AcOEt/NH_3, 99:1 to AcOEt/NH_3/MeOH, 97:1:2

Aspect: brown pale foam

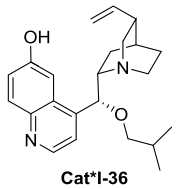
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.66 (d, *J* = 4.5 Hz, 1H), 8.14 – 8.04 (m, 1H), 7.79 – 7.65 (m, 2H), 7.52 – 7.39 (m, 4H), 7.36 – 7.23 (m, 2H), 7.25 – 7.21 (m, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.25 (ddd, *J* = 16.9, 10.4, 7.5 Hz, 1H), 6.16 (d, *J* = 3.0 Hz, 1H), 5.23 – 5.09 (m, 2H), 4.01 (s, 3H), 3.38 (m, 1H), 3.29 – 3.19 (m, 1H), 3.06 – 2.91 (m, 2H), 2.88 – 2.75 (m, 1H), 2.44 – 2.22 (m, 2H), 1.89 – 1.82 (m, 1H), 1.64 – 1.47 (m, 2H), 1.35 – 1.18 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 158.3, 155.0, 147.8, 144.8, 143.7, 140.9, 134.3, 132.3, 129.8, 129.2, 127.6, 127.0, 126.6, 126.5, 124.0, 122.0, 118.8, 118.6, 114.8, 109.1, 100.9, 79.7, 60.0, 55.9, 50.6, 50.0, 40.3, 28.5, 26.7, 21.3.

IR: 3060 (w), 2936 (w), 2872 (w), 1621 (s), 1509 (s), 1467 (m), 1254 (s), 1216 (s), 1178 (s), 998 (m), 910 (m), 836 (s), 732 (s).

HRMS: (ESI) calcd for $C_{30}H_{31}N_2O_2^+$ $[M+H]^+$ 451.2380; found 451.2374.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$ = - 150 (*c* 1.1, $CHCl_3$)



Cat*I-36

Procedure D:

Yield: 65%, Eluent: AcOEt/NH_3, 99:1 to AcOEt/NH_3/MeOH, 97:1:2

Aspect: brown pale foam

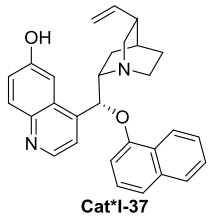
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.69 (d, *J* = 4.5 Hz, 1H), 8.31 (br s, 1H), 8.13 – 8.07 (m, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 7.39 (d, *J* = 4.4 Hz, 1H), 7.32 (dd, *J* = 9.1, 2.4 Hz, 1H), 5.61 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H), 5.46 – 5.35 (m, 1H), 4.97 – 4.82 (m, 2H), 3.75 – 3.59 (m, 1H), 3.32 – 3.16 (m, 1H), 3.07 (d, *J* = 6.3 Hz, 2H), 3.04 – 2.96 (m, 1H), 2.95 – 2.86 (m, 1H), 2.69 – 2.57 (m, 1H), 2.46 – 2.32 (m, 1H), 2.13 – 2.01 (m, 1H), 1.98 – 1.89 (m, 1H), 1.89 – 1.82 (m, 1H), 1.70 – 1.56 (m, 1H), 1.50 – 1.38 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.0, 146.8, 144.2, 143.9, 140.7, 131.4, 128.1, 123.4, 118.0, 115.3, 107.3, 78.2, 76.1, 59.7, 56.4, 43.5, 39.4, 29.0, 27.9, 27.0, 19.8, 19.7, 19.6.

IR: 2952 (w), 2935 (w), 2871 (w), 1618 (m), 1510 (w), 1467 (s), 1403 (w), 1240 (s), 1106 (s), 1060 (m), 855 (s), 822 (s), 763 (m).

HRMS: (ESI) calcd for $C_{23}H_{31}N_2O_2^+$ $[M+H]^+$ 367.2380; found 367.2388.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$ = - 81 (*c* 0.1, $CHCl_3$)



Cat*I-37

Procedure D:

Yield: 57%, Eluent: AcOEt/NH_3, 99:1 to AcOEt/NH_3/MeOH, 98:1:1

Aspect: brown pale foam

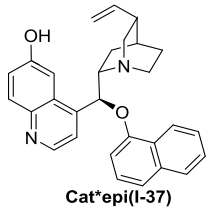
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.54 – 8.48 (m, 2H), 8.47 – 8.42 (m, 1H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.54 – 7.48 (m, 1H), 7.33 (d, *J* = 4.5 Hz, 1H), 7.23 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.37 (s, 1H), 6.21 – 6.09 (m, 1H), 5.83 – 5.68 (m, 2H), 5.18 – 4.92 (m, 2H), 3.75 – 3.57 (m, 1H), 3.51 – 3.41 (m, 1H), 3.39 – 3.28 (m, 1H), 3.02 – 2.87 (m, 2H), 2.59 – 2.45 (m, 2H), 2.31 – 2.16 (m, 1H), 2.14 – 2.08 (m, 1H), 1.85 – 1.71 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.0, 151.2, 147.2, 144.1, 142.1, 140.4, 134.7, 132.1, 128.1, 127.1, 126.5, 125.8, 125.7, 125.7, 124.0, 121.2, 120.9, 117.7, 115.8, 108.0, 106.3, 76.0, 59.4, 56.4, 43.7, 39.2, 28.0, 27.3, 20.4.

IR: 2934 (w), 1629 (m), 1599 (m), 1510 (m), 1466 (m), 1253 (s), 1215 (s), 1177 (s), 1001 (w), 835 (s), 812 (s), 745 (s).

HRMS: (ESI) calcd for $C_{29}H_{29}N_2O_2^+$ [M+] 437.2224; found 437.2221.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$ = + 243 (*c* 0.09, $CHCl_3$)



Cat*epi(I-37)

Procedure D:

Yield: 55%, Eluent: AcOEt/NH_3, 99:1 to AcOEt/NH_3/MeOH, 98:1:1

Aspect: brown pale foam

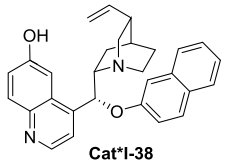
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.45 (d, *J* = 4.5 Hz, 1H), 8.42 – 8.35 (m, 1H), 8.28 – 8.17 (br s, 1H), 7.88 (d, *J* = 9.1 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.58 – 7.42 (m, 2H), 7.33 – 7.20 (m, 3H), 6.83 – 6.50 (m, 2H), 6.24 (d, *J* = 7.8 Hz, 1H), 5.65 (ddd, *J* = 17.3, 10.3, 7.0 Hz, 1H), 5.09 – 4.96 (m, 2H), 3.84 – 3.68 (m, 1H), 3.66 – 3.53 (m, 1H), 3.47 – 3.32 (m, 1H), 3.19 – 3.07 (m, 1H), 3.06 – 2.93 (m, 1H), 2.66 – 2.49 (m, 2H), 2.38 – 2.22 (m, 1H), 2.19 – 2.10 (m, 1H), 1.91 – 1.80 (m, 1H), 1.80 – 1.71 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.0, 150.8, 147.0, 144.2, 140.4, 138.7, 134.8, 132.3, 128.4, 126.7, 126.5, 126.1, 125.9, 125.6, 123.4, 121.6, 120.9, 117.7, 116.9, 107.1, 105.7, 74.4, 59.8, 55.7, 43.8, 38.2, 27.6, 26.1, 19.8.

IR: 2940 (w), 1620 (w), 1574 (w), 1509 (w), 1463 (w), 1396 (w), 1264 (w), 1236 (w), 1096 (w), 906 (s), 726 (s).

HRMS: (ESI) calcd for $C_{29}H_{29}N_2O_2^+$ $[M+H]^+$ 437.2224; found 437.2224.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$ = - 171 (*c* 0.7, $CHCl_3$)



Cat*I-38

Procedure D:

Yield: 83%, Eluent: AcOEt/NH_3, 99:13 to AcOEt/NH_3/MeOH, 97:1:2

Aspect: brown pale foam

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.57 (d, *J* = 4.5 Hz, 1H), 8.41 (d, *J* = 2.5 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 9.0, 1H), 7.39 (d, *J* = 4.5 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.19 (m, 1H), 7.15 – 7.07 (m, 2H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.70 (d, *J* = 2.5 Hz, 1H), 6.32 (s, 1H), 5.68 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H), 5.02 – 4.90 (m, 2H), 3.64 – 3.52 (m, 1H), 3.36 – 3.29 (m, 1H), 3.29 – 3.20 (m, 1H), 2.91 – 2.78 (m,

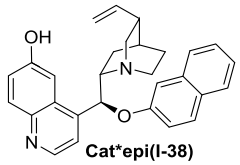
1H), 2.77 – 2.69 (m, 1H), 2.45 – 2.36 (m, 1H), 2.34 – 2.25 (m, 1H), 2.20 – 2.10 (m, 1H), 2.00 – 1.95 (m, 1H), 1.74 – 1.65 (m, 1H), 1.64 – 1.53 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$) δ 157.1, 154.2, 147.0, 143.9, 142.5, 140.5, 134.2, 131.8, 129.8, 129.2, 127.5, 127.1, 126.9, 126.5, 124.1, 123.6, 118.2, 118.0, 115.4, 109.1, 107.5, 76.9, 59.3, 56.5, 43.5, 39.4, 28.0, 27.0, 20.1

IR: 2934 (w), 2866 (w), 1733 (w), 1629 (m), 1599 (m), 1510 (s), 1466 (s), 1253 (s), 1177 (s), 1001 (w), 835 (s), 812 (s), 751 (s).

HRMS: (ESI) calcd for $C_{29}H_{29}N_2O_2^+$ $[M+H]^+$ 437.2224; found 437.2235.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$ = + 263 (*c* 0.1, $CHCl_3$)



Cat*epi(I-38)

Procedure D:

Yield: 61%, Eluent: AcOEt/NH_3, 99:1 to AcOEt/NH_3/MeOH, 98:1:1

Aspect: brown pale foam

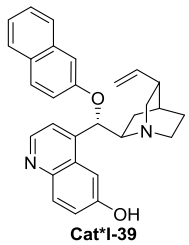
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.69 (d, *J* = 4.4 Hz, 1H), 8.12 – 7.96 (m, 2H), 7.55 – 7.47 (m, 2H), 7.39 – 7.28 (m, 3H), 7.24 – 7.14 (m, 2H), 7.14 – 7.07 (m, 1H), 7.05 – 6.97 (m, 1H), 5.63-5.56 (m, 2H), 5.02 – 4.86 (m, 2H), 3.90 – 3.69 (m, 1H), 3.31 – 3.13 (m, 2H), 2.83 – 2.65 (m, 2H), 2.30 – 2.12 (m, 1H), 1.69 – 1.61 (m, 1H), 1.61 – 1.51 (m, 1H), 1.48 – 1.34 (m, 2H), 1.18 – 1.07 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.2, 155.5, 146.2, 143.8, 142.4, 140.9, 134.0, 131.7, 129.4, 129.3, 128.4, 127.5, 126.8, 126.3, 124.0, 123.4, 122.5, 121.6, 119.6, 115.3, 109.6, 105.2, 60.4, 56.0, 41.2, 39.5, 27.5, 27.5, 24.6.

IR: 2936 (w), 1732 (w), 1629 (w), 1619 (w), 1600 (w), 1510 (m), 1467 (m), 1244 (s), 1215 (s), 1176 (m), 1044 (m), 990 (m), 836 (s), 748 (s).

HRMS: (ESI) calcd for $C_{29}H_{29}N_2O_2^+$ $[M+H]^+$ 437.2224; found 437.2203.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = - 2 (*c* 1.0, $CHCl_3$)



Cat*I-39

Procedure D:

Yield: 88%, Eluent: AcOEt/NH_3, 99:1 to AcOEt/NH_3/MeOH, 97:1:2

Aspect: brown pale foam

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.55 (d, *J* = 4.5 Hz, 1H), 8.18 (d, *J* = 3.1 Hz, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.36 (d, *J* = 4.5 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.19 – 7.14 (m, 1H), 7.11 – 7.02 (m, 2H), 6.98 – 6.89 (m, 1H), 6.71 – 6.63 (m, 1H), 6.39 – 6.34 (m, 1H), 6.34 – 6.23 (m, 1H), 5.37 – 5.01 (m, 2H), 3.64 – 3.46 (m, 1H), 3.35 – 3.15 (m, 1H), 3.11 – 2.92 (m, 2H), 2.88 – 2.73 (m, 1H), 2.64 – 2.48 (m, 1H), 2.38 – 2.24 (m, 1H), 1.93 – 1.84 (m, 1H), 1.66 – 1.53 (m, 1H), 1.52 – 1.41 (m, 1H), 1.32 – 1.16 (m, 1H).

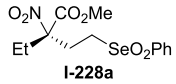
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.1, 154.4, 146.9, 144.0, 142.4, 140.1, 134.1, 131.9, 129.7, 129.1, 127.4, 127.0, 126.9, 126.4, 124.0, 123.6, 118.2, 118.2, 115.6, 109.1, 106.8, 77.6, 58.9, 50.0, 49.4, 39.7, 28.2, 26.0, 20.0.

IR: 3061 (w), 2939 (w), 1630 (m), 1600 (m), 1510 (m), 1467 (m), 1254 (s), 1216 (s), 1178 (s), 998 (w), 910 (m), 836 (s), 732 (s).

HRMS: (ESI) calcd for $C_{29}H_{29}N_2O_2^+$ $[M+H]^+$ 437.2224; found 437.2219.

$[\alpha]_D^{26}$ = - 174 (*c* 1.0, $CHCl_3$)

α,α-disubstituted α-nitroacetates



I-228a

Procedure E:

Yield: 17.4 mg, 96% Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

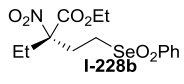
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.02 – 7.95 (m, 2H), 7.78 – 7.73 (m, 1H), 7.71 – 7.65 (m, 2H), 3.82 (s, 3H), 3.56 – 3.45 (m, 2H), 2.81 – 2.73 (m, 2H), 2.37 – 2.17 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.1, 141.0, 134.9, 130.7, 127.1, 95.0, 54.1, 54.1, 28.9, 26.7, 8.2.

IR: 3056 (w), 2941 (w), 1784 (m), 1751 (m), 1552 (s), 1443 (m), 1253 (w), 1183 (w), 884 (m), 842 (m), 744 (s), 688 (m).

HRMS: (ESI) calcd for $C_{13}H_{17}NNaO_6Se^+$ $[M+Na]^+$ 386.0113; found 386.0120.

e.r.: 95.8:4.2, $[\alpha]_D^{26}$= - 37 (*c* 0.12, $CHCl_3$)



I-228b

Procedure E:

Yield: 35 mg, 93% Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.06 – 7.92 (m, 2H), 7.79 – 7.73 (m, 1H), 7.72 – 7.65 (m, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.61 – 3.44 (m, 2H), 2.86 – 2.65 (m, 2H), 2.40 – 2.12 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H).

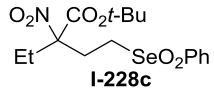
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 165.5, 141.0, 134.9, 130.7, 127.1, 95.0, 63.6, 54.2, 28.9, 26.7, 14.0, 8.2.

IR: 2997 (w), 2362 (w), 1746 (s), 1552 (s), 1446 (w), 1250 (m), 941 (s), 887 (m), 747 (m), 685 (w).

HRMS: (ESI) calcd for $C_{14}H_{19}NNaO_6Se^+$ $[M+Na]^+$ 400.0270; found 400.0259.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= - 11 (*c* 1.30, $CHCl_3$)

e.r.: 94.7:5.3



I-228c

Procedure E:

Yield: 30.9 mg, 76% Eluent: AcOEt/PE, 20:80 to 80:20

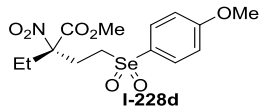
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.07 – 7.96 (m, 2H), 7.80 – 7.73 (m, 1H), 7.72 – 7.66 (m, 2H), 3.54-3.47 (m, 2H), 2.85 – 2.61 (m, 2H), 2.32 – 2.13 (m, 2H), 1.46 (s, 9H), 0.94 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 164.3, 141.0, 134.9, 130.7, 127.2, 95.4, 85.6, 54.3, 28.7, 27.8, 26.6, 8.2.

IR: 2927 (w), 2362 (s), 2336 (s), 1740 (w), 1442 (w), 1065 (w), 855 (w), 744 (m), 672 (m), 640 (m).

HRMS: (ESI) calcd for $C_{16}H_{23}NNaO_6Se^+$ $[M+Na]^+$ 428.0583; found 428.0581.



I-228d

Procedure E: Yield: quant., Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.89 (d, *J* = 9.0 Hz, 2H), 7.12 (d, *J* = 9.0 Hz, 2H), 3.91 (s, 3H), 3.82 (s, 3H), 3.50 – 3.42 (m, 2H), 2.86 – 2.60 (m, 2H), 2.44 – 2.06 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H).

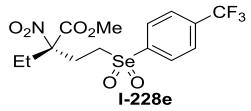
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.0, 164.5, 131.6, 129.0, 115.7, 94.9, 55.9, 54.1, 53.9, 28.7, 26.6, 8.1.

IR: 2954 (w), 1751 (m), 1588 (m), 1554 (s), 1494 (m), 1262 (s), 1023 (w), 938 (w), 886 (m), 834 (w).

HRMS: (ESI) calcd for $C_9H_{13}O_3^+$ $[M+H]^+$ 169.0859; found 169.0858.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= - 42 (*c* 0.36, $CHCl_3$)

e.r.: 95.4:4.6



I-228e

Procedure E: Yield: 67%, Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): 8.15 (d, *J* = 8.2 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 2H), 3.84 (s, 3H), 3.63 – 3.56 (m, 2H), 2.80 – 2.76 (m, 2H), 2.32 – 2.17 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H).

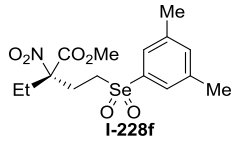
^{13}C NMR (100.62 MHz, $CDCl_3$): 165.9, 144.3, 136.5 (q, *J* = 33.5 Hz), 127.9, 127.6 (q, *J* = 3.7 Hz), 122.8 (q, *J* = 273.5 Hz), 94.8, 54.6, 54.0, 28.9, 26.5, 8.1.

IR: 2927 (w), 2325 (m), 2103 (w), 1906 (w), 1558 (w), 1325 (m), 1137 (m), 1048 (s), 889 (w), 667 (m).

HRMS: (ESI) calcd for $C_{14}H_{16}F_3NO_6Se$ [M+] 431.0095; found.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= - 50 (*c* 0.31, $CHCl_3$)

e.r.: 90.8:9.2



I-228f

Procedure E: Yield: 90%, Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

^{1}H NMR (400.13 MHz, CDCl): δ 7.57 – 7.55 (m, 2H), 7.35 – 7.34 (m, 1H), 3.83 (s, 3H), 3.56 – 3.39 (m, 2H), 2.87 – 2.69 (m, 2H), 2.43 (s, 6H), 2.37 – 2.16 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.1, 141.1, 140.6, 136.6, 124.3, 95.1, 54.0, 53.9, 28.9, 26.7, 21.5, 8.2.

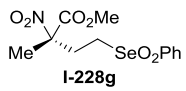
IR: 2960 (w), 2922 (w), 1752 (m), 1555 (s), 1440 (w), 1255 (w), 945 (w), 890 (m).

HRMS: (ESI) calcd for $C_{15}H_{21}NO_6Se$ [M+] 391.0534; found.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= - 36 (*c* 0.41, $CHCl_3$)

e.r.: 93.9:6.1

e.r.: 54.3:45.7



I-228g

Procedure E:

Yield: 16.5 mg, 95%, Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

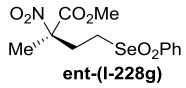
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.03 – 7.95 (m, 2H), 7.80 – 7.72 (m, 1H), 7.72 – 7.63 (m, 2H), 3.82 (s, 3H), 3.62 – 3.52 (m, 2H), 2.87 – 2.68 (m, 2H), 1.85 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.5, 141.0, 134.9, 130.7, 127.1, 91.0, 54.2, 54.1, 29.5, 22.4.

IR: 2957 (w), 1750 (s), 1554 (s), 1447 (m), 1271 (m), 1065 (w), 938 (m), 886 (m), 747 (w), 686 (w).

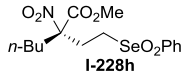
HRMS: (ESI) calcd for $C_{12}H_{15}NNaO_6Se^+$ $[M+Na]^+$ 371.9957; found 371.9955.

e.r.: 97.9:2.1, $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= - 38 (*c* 0.1, $CHCl_3$)



ent-(I-228g)

e.r.: 95.4:4.6, $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= + 7 (*c* 1.66, $CHCl_3$)



I-228h

Procedure E:

Yield: 19.5 mg, quantitative yield Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.02 – 7.93 (m, 2H), 7.78 – 7.72 (m, 1H), 7.71 – 7.64 (m, 2H), 3.81 (s, 3H), 3.57 – 3.43 (m, 2H), 2.84 – 2.70 (m, 2H), 2.29 – 2.11 (m, 2H), 1.37 – 1.32 (m, 2H), 1.16 – 1.26 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

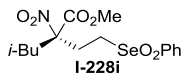
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.2, 141.0, 134.9, 130.7, 127.1, 94.6, 54.2, 54.0, 35.2, 27.1, 25.7, 22.5, 13.7.

IR: 2960 (w), 2934 (w), 1751 (m), 1553 (s), 1446 (w), 1255 (w), 1221 (w), 1066 (w), 941 (m), 887 (m), 746 (w), 686 (w).

HRMS: (ESI) calcd for $C_{15}H_{21}NNaO_6Se^+$ $[M+Na]^+$ 414.0426; found 414.0441.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$= - 14.46 (*c* 0.74, $CHCl_3$)

e.r.: 96.5:3.5



I-228i

Procedure E:

Yield: 19.5 mg, quantitative yield, Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

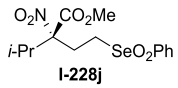
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.02 – 7.94 (m, 2H), 7.80 – 7.71 (m, 1H), 7.73 – 7.64 (m, 2H), 3.81 (s, 3H), 3.57 – 3.38 (m, 2H), 2.88 – 2.72 (m, 2H), 2.29 – 2.09 (m, 2H), 1.72– 1.64 (m, 2H), 0.90 (m, 6H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.4, 141.0, 134.9, 130.7, 127.2, 94.4, 54.3, 54.0, 43.4, 27.4, 24.2, 23.4, 23.3.

IR: 2963 (w), 1751 (m), 1554 (s), 1446 (w), 1244 (w), 941 (m), 887 (m), 747 (w), 685 (w).

HRMS: (ESI) calcd for $C_{15}H_{21}NNaO_6Se^+$ $[M+Na]^+$ 414.0426; found 414.0433.

e.r.: 92.1:7.9, $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= - 32 (*c* 0.47, $CHCl_3$)



I-228j

Procedure E: Yield: quantitative, Eluent: AcOEt/PE 20:80 to 80:20

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.02 – 7.95 (m, 2H), 7.80 – 7.71 (m, 1H), 7.72 – 7.63 (m, 2H), 3.82 (s, 3H), 3.65 – 3.51 (m, 2H), 2.82 – 2.71 (m, 2H), 2.70 – 2.63 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H).

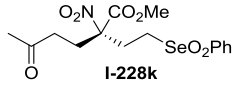
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 165.7, 141.1, 134.8, 130.6, 127.1, 98.3, 54.8, 53.8, 35.1, 26.2, 18.0, 17.7.

IR: 2977 (w), 2956 (w), 1749 (m), 1551 (s), 1446 (w), 1258 (m), 940 (m), 887 (m), 747 (w), 686 (w).

HRMS: (ESI) calcd for $C_{14}H_{19}NNaO_6Se^+$ $[M+Na]^+$ 400.0270; found 400.0276.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= + 2 (*c* 1.1, $CHCl_3$)

e.r.: 45.4:54.6



I-228k

Procedure E:

Yield: 20.0 mg, 84%, Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

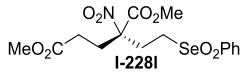
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.04 – 7.95 (m, 2H), 7.79 – 7.72 (m, 1H), 7.69 (m, 2H), 3.82 (s, 3H), 3.57 – 3.49 (m, 2H), 2.83 – 2.71 (m, 2H), 2.60 – 2.53 (m, 2H), 2.53 – 2.46 (m, 2H), 2.15 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 205.3, 165.8, 141.0, 134.9, 130.7, 127.2, 93.7, 54.3, 53.9, 37.6, 30.1, 28.6, 27.6.

IR: 3063 (w), 2956 (w), 1750 (s), 1717 (m), 1555 (s), 1446 (m), 1358 (w), 1260 (w), 941 (m), 887 (m), 747 (w), 687 (w).

HRMS: (ESI) calcd for $C_{15}H_{19}NNaO_7Se^+$ $[M+Na]^+$ 428.0219; found 428.0221.

e.r.: 95.8:4.2, $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= - 22 (*c* 0.55, $CHCl_3$)



I-228l

Procedure E:

Yield: 21.0 mg, quantitative yield, Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.01 – 7.95 (m, 2H), 7.78 – 7.73 (m, 1H), 7.73 – 7.65 (m, 2H), 3.83 (s, 3H), 3.69 (s, 3H), 3.58 – 3.49 (m, 2H), 2.80 – 2.72 (m, 2H), 2.61 – 2.53 (m, 2H), 2.41 (m, 2H).

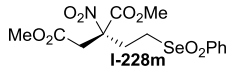
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 171.8, 165.6, 141.0, 134.9, 130.7, 127.2, 93.6, 54.3, 53.9, 52.4, 30.1, 28.5, 27.5.

IR: 2956 (w), 1738 (s), 1555 (s), 1445 (m), 1350 (w), 1266 (m), 1205 (m), 939 (s), 886 (s), 747 (m), 687 (w).

HRMS: (ESI) calcd for $C_{15}H_{19}NNaO_8Se^+$ $[M+Na]^+$ 444.0168; found 444.0169.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= + 2 (*c* 2.1, $CHCl_3$)

e.r.: 92.7:7.3



I-228m

Procedure E: Yield: 95%, Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.04 – 7.93 (m, 2H), 7.80 – 7.73 (m, 1H), 7.73 – 7.65 (m, 2H), 3.85 (s, 3H), 3.71 (s, 3H), 3.65 – 3.59 (m, 2H), 3.36 (d, *J* = 17.1 Hz, 1H), 3.30 (d, *J* = 17.1 Hz, 1H), 3.00 – 2.91 (m, 2H).

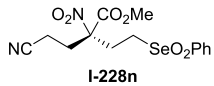
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.0, 165.0, 140.9, 134.9, 130.7, 127.2, 91.2, 54.6, 54.2, 52.9, 39.6, 27.8.

IR: 2957 (w), 1742 (s), 1561 (s), 1440 (m), 1370 (w), 1213 (m), 941 (m), 887 (m), 748 (w), 686 (w).

HRMS: (ESI) calcd for $C_{14}H_{17}NNaO_8Se^+$ $[M+Na]^+$ 430.0012; found 430.0009.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= + 20 (*c* 0.8, $CHCl_3$)

e.r.: 86.8:13.2



I-228n

Procedure E:

Yield: 16.6 mg, 86%, Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.00 – 7.88 (m, 2H), 7.73 – 7.67 (m, 1H), 7.65-7.61 (m, 2H), 3.83 (s, 3H), 3.60 – 3.36 (m, 2H), 2.90 – 2.69 (m, 2H), 2.62 – 2.39 (m, 4H).

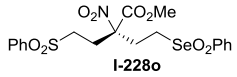
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 164.8, 140.9, 134.9, 130.7, 127.2, 117.4, 91.2, 54.6, 54.2, 52.9, 39.6, 27.8.

IR: 2957 (w), 2927 (w), 2359 (w), 2252 (w), 1749 (s), 1556 (s), 1446 (m), 1260 (m), 1220 (m), 938 (s), 885 (s), 746 (m), 685 (m).

HRMS: (ESI) calcd for $C_{14}H_{16}N_2NaO_6Se^+$ $[M+Na]^+$ 411.0066; found 411.0063.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= + 2 (*c* 1.3, $CHCl_3$)

e.r.: 91.3:8.7



I-228o

Procedure E:

Yield: 22.6 mg, 90% yield Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

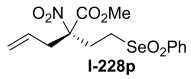
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.02 – 7.96 (m, 2H), 7.96 – 7.90 (m, 2H), 7.80 – 7.73 (m, 1H), 7.72 – 7.67 (m, 3H), 7.65 – 7.58 (m, 2H), 3.83 (s, 3H), 3.61 – 3.42 (m, 2H), 3.27 – 3.14 (m, 2H), 2.86 – 2.75 (m, 2H), 2.71 – 2.60 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 165.0, 140.9, 138.2, 135.0, 134.6, 130.8, 129.8, 128.2, 127.2, 92.7, 54.6, 53.4, 50.8, 28.3, 27.6.

IR: 3063 (w), 1751 (s), 1558 (s), 1447 (m), 1309 (m), 1149 (s), 1088 (w), 940 (m), 887 (m), 745 (m), 687 (m).

HRMS: (ESI) calcd for $C_{19}H_{21}NNaO_8SSe^+$ $[M+Na]^+$ 526.0045; found 526.0046.

e.r.: 87.0:13.0, $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= + 2 (*c* 1.43, $CHCl_3$)



I-228p

Procedure E:

Yield: 18.1 mg, 97%, Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.02 – 7.94 (m, 2H), 7.79 – 7.73 (m, 1H), 7.72 – 7.65 (m, 2H), 5.58 (ddt, *J* = 16.6, 10.4, 7.3 Hz, 1H), 5.28 – 5.20 (m, 2H), 3.83 (s, 3H), 3.60 – 3.48 (m, 2H), 3.07 – 2.89 (m, 2H), 2.78 – 2.68 (m, 2H).

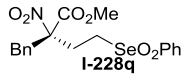
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 165.7, 141.0, 134.9, 130.7, 128.3, 127.2, 123.0, 93.8, 54.2, 54.0, 40.0, 27.1.

IR: 2960 (w), 2927 (w), 1752 (m), 1555 (s), 1446 (m), 1258 (w), 940 (s), 887 (m), 747 (w), 686 (w).

HRMS: (ESI) calcd for $C_{14}H_{17}NNaO_6Se^+$ $[M+Na]^+$ 398.0113; found 398.0109.

$[\alpha]_D^{25}$= - 25 (*c* 0.31, $CHCl_3$)

e.r.: 95.1:4.9



I-228q

Procedure E: Yield: 95%, Eluent: AcOEt/PE, 20:80 to 80:20

Gram scale procedure: To a solution of phenyl vinyl selenone (**2a**) (1.23 g, 5.7 mmol, 1 equiv) and **QN-7** (250 mg, 0.057 mmol, 0.1 equiv) in toluene (5 mL) at - 30 °C was added a solution of α-substituted nitroacetate **4m** (1.31 g, 6.3 mmol, 1.1 equiv) in toluene (1 mL)**.** The reaction mixture was stirred at - 30 °C until complete consumption of the starting material (TLC monitoring, around 72 hours). The reaction mixture was warmed to room temperature and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product. The catalyst was recovered in 96% yield (240 mg) by using AcOEt/MeOH/NH_3 100:2:1 as eluent.

Aspect: yellow oil

^{1}H NMR (400.13 MHz, CDCl): δ 7.98 – 7.87 (m, 2H), 7.78 – 7.68 (m, 1H), 7.69 – 7.60 (m, 2H), 7.33 – 7.25 (m, 3H), 7.07 – 6.99 (m, 2H), 3.84 (s, 3H), 3.62 (d, *J* = 14.3 Hz, 1H), 3.50 (d, *J* = 14.3 Hz, 1H) 3.50 – 3.46 (m, 2H) 2.71 – 2.57 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 165.8, 140.8, 134.8, 131.6, 130.6, 130.0, 129.3, 128.6, 127.2, 94.9, 54.2, 54.2, 41.6, 26.9.

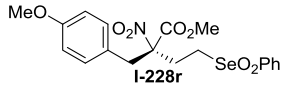
^{77}Se NMR (76.31 MHz, $Se(Me)_2$): 995.9

IR: 2940 (w), 1749 (m), 1552 (s), 1438 (m), 938 (m), 885 (m), 744 (s), 683 (m).

HRMS: (ESI) calcd for $C_{18}H_{19}NNaO_6Se^+$ $[M+Na]^+$ 448.0270; found 448.0269.

$[\alpha]_D^{26}$= - 10 (*c* 0.59, $CHCl_3$)

e.r.: 91.1:8.9



I-228r

Procedure E: Yield: 88%, Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

^{1}H NMR (400.13 MHz, CDCl): δ 7.97 – 7.88 (m, 2H), 7.77 – 7.69 (m, 1H), 7.68 – 7.60 (m, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.57 (d, *J* = 14.5 Hz, 1H) 3.52 – 3.46 (m, 2H) 3.45 (d, *J* = 14.5 Hz, 1H), 2.68 – 2.59 (m, 2H).

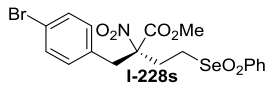
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 165.9, 159.7, 140.9, 134.8, 131.1, 130.6, 127.2, 123.4, 114.6, 95.0, 55.4, 54.3, 54.1, 40.9, 26.8.

IR: 2958 (w), 1752 (m), 1554 (s), 1514 (s), 1252 (s), 941 (s), 886 (s), 743 (m), 686 (m).

HRMS: (ESI) calcd for $C_{19}H_{21}NNaO_7Se^+$ $[M+Na]^+$ 478.0375; found 478.0373.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= - 44.0 (*c* 0.49, $CHCl_3$)

e.r.: 90.5:9.5



I-228s

Procedure E: Yield: 85%, Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

^{1}H NMR (400.13 MHz, CDCl): δ 7.94 – 7.84 (m, *J* = 8.3 Hz, 2H), 7.75 – 7.68 (m, 1H), 7.66 – 7.57 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.32 (m, 2H), 6.95 – 6.85 (m, 2H), 3.81 (s, 3H), 3.57 (d, *J* = 14.4 Hz, 1H), (3.55 – 3.50 (m, 2H), 3.46 (d, *J* = 14.4 Hz, 1H), 2.68 – 2.49 (m, 2H).

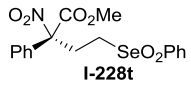
^{13}C NMR (100.62 MHz, $CDCl_3$): = 165.5, 140.6, 134.8, 132.3, 131.6, 130.7, 130.6, 130.5, 130.5, 127.2, 127.1, 127.0, 122.8, 94.5, 54.2, 53.9, 40.8, 26.7.

IR: 2956 (w), 1751 (m), 1555 (s), 1446 (w), 1257 (w), 941 (m), 886 (s), 729 (s).

HRMS: (ESI) calcd for $C_{18}H_{18}BrNNaO_6Se^+$ $[M+Na]^+$ 525.9375; found 525.9383.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26}}$= - 31 (*c* 0.11, $CHCl_3$)

e.r.: 90.7:9.3



I-228t

Procedure E: Yield: 83%, Eluent: AcOEt/PE, 20:80 to 80:20

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.03 – 7.91 (m, 2H), 7.79 – 7.72 (m, 1H), 7.72 – 7.63 (m, 2H), 7.51 – 7.40 (m, 3H), 7.31 – 7.26 (m, 2H), 3.88 (s, 3H), 3.60 (m, 1H), 3.41 (m, 1H), 3.34 – 3.14 (m, 2H).

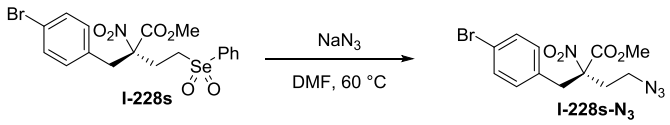
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.0, 141.0, 134.9, 131.6, 130.7, 130.6, 129.4, 127.5, 127.2, 97.2, 54.7, 54.4, 29.3.

IR: 3061 (w), 2956 (w), 1748 (s), 1557 (s), 1446 (m), 1353 (w), 1253 (m), 939 (s), 885 (s), 741 (s), 686 (m).

HRMS: (ESI) calcd for $C_{17}H_{17}NNaO_6Se^+$ $[M+Na]^+$ 434.0113; found 434.0121.

e.r.: 60.6:39.4

Further chemical transformation of compounds **I-228**



Procedure: To a solution of the selenone **5o** (362.3 mg, 0.72 mmol, 1 equiv) in DMF (10 mL) was added NaN_3 (61.1 mg, 0.94 mmol, 1.3 equiv). The reaction mixture was stirred at 60 °C until complete consumption of the starting material (TLC monitoring, around 2 hours). The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 212 mg, 83%, Eluent: AcOEt/PE, 10:90 to 20:80

Aspect: yellow oil

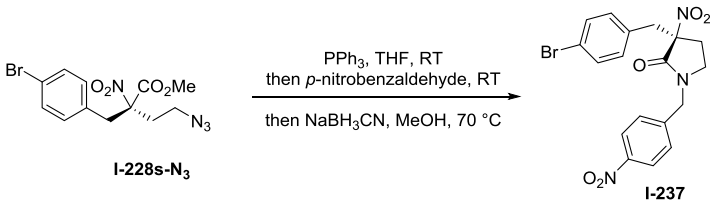
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.51 – 7.38 (m, 2H), 7.01 – 6.90 (m, 2H), 3.85 (s, 3H), 3.63 (d, *J* = 14.4 Hz, 1H), 3.50 – 3.42 (m, 3H), 2.39 – 2.18 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.5, 132.3, 131.7, 131.5, 122.6, 94.4, 53.9, 46.7, 40.4, 32.8.

IR: 2956 (w), 2100 (s), 1752 (m), 1553 (s), 1489 (w), 1260 (m), 1212 (m), 1075 (w), 1013 (w) 801 (w).

HRMS: (ESI) calcd for $C_{12}H_{13}N_2O_4Br$+ [M-N_2]+ 329.0131; found 329.0136.

$[\alpha]_D^{26}$= - 12 (*c* 0.17, $CHCl_3$)



Procedure: To a solution of azide **8o** (121.4 mg, 0.34 mmol) in THF (4 mL) was added triphenylphosphine (98.1 mg, 0.37 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 2 hours. *p*-Nitrobenzaldehyde (77.0 mg, 0.51 mmol, 1.5 equiv) was added and stirring was continued at room temperature for another 2 hours. The reaction mixture was diluted with MeOH (1 mL) and $NaBH_3CN$ (42.7 mg, 0.68 mmol, 2 equiv) was added. After being stirred at 70 °C for 16 hours, the reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 50 mg, 34% yield, Eluent: AcOEt/PE, 50:50 to 70:30

Aspect: pale yellow solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.21 – 8.14 (m, 2H), 7.47 – 7.40 (m, 2H), 7.24 – 7.19 (m, 2H), 7.17 – 7.11 (m, 2H), 4.59 (d, *J* = 15.4 Hz, 1H), 4.50 (d, *J* = 15.4 Hz, 1H), 3.70 (d, *J* = 13.6 Hz, 1H), 3.47 (d, *J* = 13.6 Hz,

1H), 3.45 – 3.37 (m, 1H), 2.86 (ddd, *J* = 9.5, 8.8, 3.1 Hz, 1H), 2.69 (ddd, *J* = 14.7, 8.0, 3.1 Hz, 1H), 2.37 (ddd, *J* = 14.6, 8.9, 6.7 Hz, 1H).

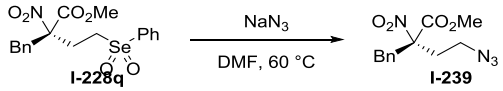
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.6, 147.9, 142.1, 132.3, 132.2, 132.2, 128.7, 124.3, 122.3, 93.7, 47.0, 44.0, 38.4, 28.3.

IR: 2922 (m), 2853 (w), 1708 (m), 1547 (s), 1520 (w), 1345 (s), 1262 (w), 1013 (m), 801 (m).

HRMS: (ESI) calcd for $C_{18}H_{16}N_3O_5BrNa$+ [M+Na]+ 456.0166; found 456.0162.

Melting point: 110-112 °C

$[\alpha]_D^{26}$= - 20 (*c* 0.42, $CHCl_3$)



Procedure: To a solution of selenone **5m** (190 mg, 0.67 mmol, 1 equiv) in DMF (7 mL) was added NaN_3 (57 mg, 0.87 mmol, 1.3 equiv). The reaction mixture was stirred at 60 °C until complete consumption of the starting material (TLC monitoring, around 2 hours). The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 152 mg, 83%, Eluent: AcOEt/PE, 5:95

Aspect: yellow oil

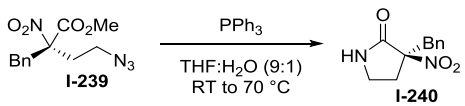
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.26 – 7.22 (m, 3H), 7.01 (d, *J* = 3.5 Hz, 2H), 3.77 (s, 3H), 3.59 (s, 1H), 3.44 (d, *J* = 14.4 Hz, 1H), 3.38 (t, *J* = 7.1 Hz, 1H), 2.40 – 2.11 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.6, 132.3, 129.9, 129.0, 128.2, 94.5, 53.7, 46.6, 40.8, 32.6.

IR: 2923 (w), 2099 (m), 1753 (m), 1553 (s), 1438 (w), 1212 (m), 1095 (w), 737 (w), 703 (m).

HRMS: (ESI) $C_{12}H_{14}N_4NaO_4$ [M+Na] 301.0913; found 301.0915.

$[\alpha]_D^{26}$= - 32 (*c* 0.28, $CHCl_3$)



Procedure: To a solution of azide **8** (135 mg, 0.5 mmol, 1 equiv) in THF/H_2O (9:1, 4.5 mL of THF + 0.5 mL of H_2O) was added PPh_3 (170 mg, 0.65 mmol, 1.3 equiv). The reaction mixture was stirred at room temperature for 2 hours and heated at 70 °C for 24 hours. The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 59 mg, 54%, Eluent: AcOEt/PE, 30:70 to 50:50

Aspect: amorphous white solid

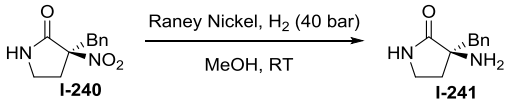
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.35 – 7.28 (m, 3H), 7.26 – 7.22 (m, 2H), 6.33 – 5.80 (m, 1H), 3.58 (s, 2H), 3.52 – 3.43 (m, 1H), 2.94 (m 1H), 2.83 (ddd, *J* = 14.5, 7.8, 3.5 Hz, 1H), 2.46 (ddd, *J* = 14.7, 8.5, 6.4 Hz, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 169.4, 133.5, 130.4, 129.0, 128.0, 93.3, 39.2, 39.2, 30.5.

IR: 3257 (w), 1717 (s), 1543 (s), 1456 (w), 1337 (w), 1283 (w), 1067 (w), 779 (w), 703 (m).

HRMS: (ESI) calcd for $C_{11}H_{12}N_2NaO_3^+$ $[M+Na]^+$ 243.0740; found 243.0746.

$[\alpha]_D^{26}$= - 42 (*c* 0.29, $CHCl_3$)



Procedure: To a solution of **9** (20 mg, 0.091 mmol, 1 equiv) in MeOH (1 mL) was added a suspension of Raney Nickel (0.5 mL) in H_2O. The resulting mixture was stirred in an autoclave under 40 bar of H_2 at room temperature for 16 hours. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 13 mg, 75% yield, Eluent: AcOEt/PE, 70:30 to 90:10

Aspect: amorphous white solid

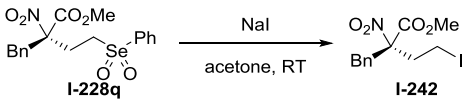
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.39 – 7.19 (m, 5H), 5.71 (s, 1H), 3.21 – 3.10 (m, 1H), 2.97 (d, *J* = 13.2 Hz, 1H), 2.80 (d, *J* = 13.2 Hz, 1H), 2.74 – 2.61 (m, 1H), 2.38 – 2.22 (m, 1H), 1.96 – 1.84 (m, 1H), 1.67 (br s, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 180.5, 136.3, 130.3, 128.5, 127.1, 59.4, 44.6, 38.2, 33.8.

IR: 3224 (w), 2359 (w), 1495 (w), 1456 (w), 1292 (w), 780 (m), 703 (s).

HRMS: (ESI) calcd for $C_{11}H_{15}N_2O^+$ $[M+H]^+$ 191.1179; found 191.1178.

$[\alpha]_D^{26}$= + 30 (*c* 0.68, $CHCl_3$)



Procedure: To a solution of **5m** (255 mg, 0.6 mmol, 1 equiv) in acetone (6 mL) was added NaI (117 mg, 0.78 mmol, 1.3 equiv). The reaction mixture was stirred at room temperature until complete consumption of the starting material (TLC monitoring, around 2 hours). The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 193 mg, 88%, Eluent: AcOEt/PE, 5:95

Aspect: yellow oil

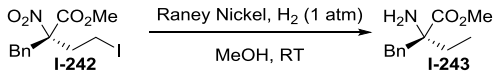
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.35 – 7.30 (m, 3H), 7.13 – 7.02 (m, 2H), 3.84 (s, 3H), 3.59 (d, *J* = 14.3 Hz, 1H), 3.49 (d, *J* = 14.3 Hz, 1H), 3.18 – 3.03 (m, 2H), 2.65-2.63 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.0, 132.2, 129.7, 129.0, 128.3, 96.7, 53.7, 40.5, 38.4, -5.8.

IR: 2955 (w), 1750 (s), 1551 (s), 1436 (w), 1252 (m), 1192 (m), 741 (w), 702 (m).

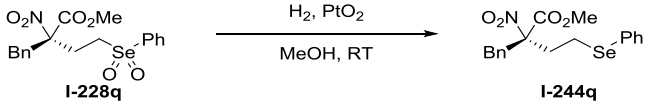
HRMS: $C_{12}H_{14}INNaO_4^+$ $[M+Na]^+$ 385.9860; found 385.9856.

$[\alpha]_D^{26}$= - 18 (*c* 0.50, $CHCl_3$)



Procedure: To a solution of iodide **11** (33 mg, 0.089 mmol, 1 equiv) in MeOH was (1 mL) added a suspension of Raney Nickel in H_2O (0.5 mL). The resulting mixture was stirred under H_2 atmosphere at room temperature for 16 hours. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude product was used without further purification.

Yield: 12 mg, 65%, Eluent: AcOEt/PE, 30:70 to 80:20



Procedure: To a solution of selenone **5m** (123 mg, 0.29 mmol, 1 equiv) in MeOH (3 mL) was added PtO_2 (16 mg, 0.06 mmol, 0.2 equiv). The resulting mixture was stirred under H_2 atmosphere at room temperature for 16 hours. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 102 mg, 91%, Eluent: AcOEt/PE, 5:95

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.44 – 7.41 (m, 2H), 7.23 – 7.21 (m, 3H), 7.17 – 7.14 (m, 3H), 6.85 – 6.83 (m, 2H), 3.70 (s, 3H), 3.54 (d, , *J* = 14.3 Hz, 1H), 3.44 (d, *J* = 14.3 Hz, 1H), 2.75 – 2.70 (m, 2H), 2.38 – 2.34 (m, 2H).

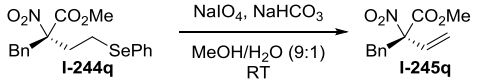
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.6, 133.8, 132.6, 129.8, 129.4, 128.9, 128.8, 128.1, 127.8, 96.4, 53.6, 40.1, 34.6, 20.9.

^{77}Se NMR (76.31 MHz, $Se(Me)_2$): δ 327.0

IR: 2954 (w), 1753 (m), 1552 (s), 1437 (m), 1358 (w), 1256 (w), 1210 (w), 740 (m), 703 (m).

HRMS: (ESI) calcd for $C_{18}H_{19}NNaO_4Se^+$ $[M+Na]^+$ 416.0371; found 416.0381.

$[\alpha]_D^{26}$= - 50 (*c* 0.27, $CHCl_3$)



Procedure: To a solution of selenide **13m** (84 mg, 0.21 mmol, 1 equiv) in MeOH/H_2O (9:1, 1.8 mL of MeOH + 0.2 mL of H_2O) was added $NaHCO_3$ (27 mg, 0.32 mmol, 1.5 equiv) and $NaIO_4$ (49 mg, 0.23 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 42 mg, 83%, Eluent: AcOEt/PE, 5:95

Aspect: yellow oil

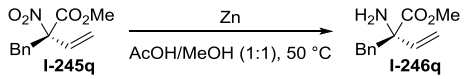
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.29 – 7.27 (m, 3H), 7.11 – 7.09 (m, 2H), 6.22 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.51 (d, *J* = 11.1 Hz, 1H), 5.35 (d, *J* = 17.7 Hz, 1H), 3.84 (s, 3H), 3.78 (d, *J* = 14.1 Hz, 1H), 3.58 (d, *J* = 14.1 Hz, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.3, 132.5, 131.5, 130.4, 128.7, 128.1, 119.5, 96.9, 53.8, 43.1.

IR: 2956 (w), 2359 (w), 1754 (m), 1556 (s), 1438 (w), 1355 (w), 1254 (w), 704 (w).

HRMS: (ESI) calcd for $C_{12}H_{13}NNaO_4^+$ $[M+Na]^+$ 258.0737; found 258.0733.

$[\alpha]_D^{26}$= - 15 (*c* 0.49, $CHCl_3$)



Procedure: To a solution of **14m** (31 mg, 0.13 mmol, 1 equiv) in AcOH/MeOH (1:1, 1 mL of AcOH + 1 mL of MeOH) was added zinc powder (170 mg, 2.6 mmol, 20 equiv). The reaction mixture was stirred at 50 °C for 16 hours. The reaction mixture was cooled down to room temperature, diluted with water and extracted with DCM (3 times). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 22 mg, 85% yield, Eluent: AcOEt/PE, 70:30 to 90:10

Aspect: yellow oil

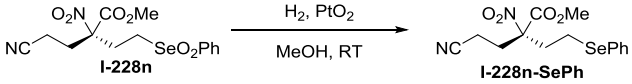
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.34 – 7.24 (m, 3H), 7.21 – 7.16 (m, 2H), 6.18 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.42 (d, *J* = 17.3 Hz, 1H), 5.26 (d, *J* = 10.7 Hz, 1H), 3.74 (s, 3H), 3.31 (d, *J* = 13.4 Hz, 1H), 2.95 (d, *J* = 13.4 Hz, 1H), 2.59 (s, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 174.3, 139.1, 135.3, 130.3, 128.6, 127.4, 115.6, 64.0, 52.7, 45.4.

IR: 2952 (w), 1736 (s), 1605 (w), 1496 (w), 1437 (w), 1201 (m), 929 (w), 744 (w), 705 (m).

HRMS: (ESI) calcd for $C_{12}H_{16}NO_2^+$ $[M+H]^+$ 206.1176; found 206.1179.

$[\alpha]_D^{26}$= - 5 (*c* 0.2, $CHCl_3$)



Procedure: To a solution of selenone **5i** (86 mg, 0.22 mmol, 1 equiv) in MeOH (2.2 mL) was added PtO_2 (10 mg, 0.044 mmol, 0.2 equiv). The resulting mixture was stirred under H_2 atmosphere at room temperature for 16 hours. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 62 mg, 79% yield, Eluent: AcOEt/PE, 10:90 to 30:70

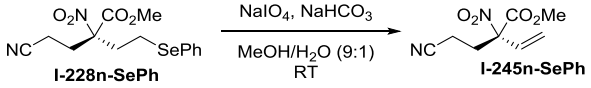
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.54 – 7.46 (m, 2H), 7.35 – 7.28 (m, 3H), 3.83 (s, 3H), 2.84 – 2.68 (m, 2H), 2.64 – 2.46 (m, 4H), 2.44 – 2.26 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 165.6, 133.5, 129.6, 128.5, 128.1, 117.6, 94.1, 54.1, 36.2, 30.4, 20.2, 12.8.

IR: 2956 (w), 2358 (w), 1750 (s), 1554 (s), 1438 (m), 1308 (m), 1149 (s), 741 (m), 690 (m).

HRMS: (ESI) calcd for $C_{14}H_{16}N_2NaO_4Se^+$ $[M+Na]^+$ 379.0167; found 379.0165.



Procedure: To a solution of selenide **13i** (60 mg, 0.17 mmol, 1 equiv) in MeOH/H_2O (9:1, 1.8 mL of MeOH + 0.2 mL of H_2O) was added $NaHCO_3$ (22 mg, 0.26 mmol, 1.5 equiv) and $NaIO_4$ (41 mg, 0.19 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 22 mg, 64% yield, Eluent: AcOEt/PE, 10:90 to 30:70

Aspect: yellow oil

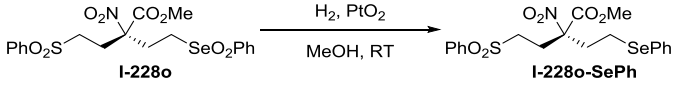
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.39 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.65 (dd, *J* = 11.0, 0.6 Hz, 1H), 5.43 (dd, *J* = 17.7, 0.6 Hz, 1H), 3.87 (s, 3H), 2.83 – 2.64 (m, 2H), 2.58 – 2.37 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 165.3, 130.1, 121.6, 117.8, 94.2, 54.3, 31.3, 12.8.

IR: 2959 (w), 2358 (w), 1752 (s), 1651 (w), 1557 (s), 1438 (w), 1254 (m), 953 (w).

HRMS: (ESI) calcd for $C_8H_{10}N_2NaO_4^+$ $[M+Na]^+$ 221.0533; found 221.0528.

$[\alpha]_D^{26}$= + 3 (*c* 0.57, $CHCl_3$)



Procedure: To a solution of selenone **5j** (65 mg, 0.13 mmol, 1 equiv) in MeOH (1.3 mL) was added PtO_2 (6 mg, 0.026 mmol, 0.2 equiv). The resulting mixture was stirred under H_2 atmosphere at room temperature for 16 hours. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 50 mg, 82% yield, eluent: AcOEt/PE, 20:80 to 30:70

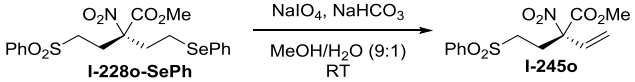
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.92 – 7.84 (m, 2H), 7.74 – 7.65 (m, 1H), 7.63 – 7.56 (m, 2H), 7.51 – 7.46 (m, 2H), 7.32 – 7.28 (m, 3H), 3.76 (s, 3H), 3.08 – 2.98 (m, 2H), 2.74 – 2.65 (m, 2H), 2.59 – 2.53 (m, 2H), 2.53 – 2.44 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 165.8, 138.4, 134.4, 133.4, 129.7, 129.6, 128.5, 128.2, 128.0, 94.1, 54.1, 51.0, 36.2, 27.6, 20.0.

IR: 2957 (w), 2365 (w), 2343 (w), 1752 (m), 1554 (s), 1447 (m), 1308 (m), 1154 (m), 741 (m), 690 (m).

HRMS: HRMS (ESI) calcd for $C_{19}H_{21}NNaO_6SSe^+$ $[M+Na]^+$ 494.0147; found 494.0150.



Procedure: To a solution of selenide **13j** (39 mg, 0.082 mmol, 1 equiv) in MeOH/H_2O (9:1, 0.9 mL of MeOH + 0.1 mL of H_2O) was added $NaHCO_3$ (10 mg, 0.12 mmol, 1.5 equiv) and $NaIO_4$ (19 mg, 0.090 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 18 mg, 70% yield Eluent: AcOEt/PE, 10:90 to 30:70

Aspect: yellow oil

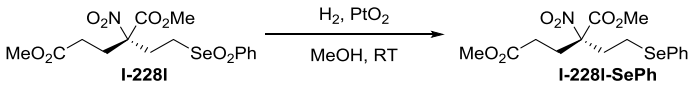
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.96 – 7.87 (m, 2H), 7.75 – 7.67 (m, 1H), 7.64 – 7.57 (m, 2H), 6.30 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.58 (dd, *J* = 11.1, 0.6 Hz, 1H), 5.37 (dd, *J* = 17.7, 0.6 Hz, 1H), 3.82 (s, 3H), 3.24 – 3.02 (m, 2H), 2.80 – 2.70 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 165.4, 138.4, 134.4, 130.1, 129.7, 128.2, 121.6, 94.2, 54.2, 51.2, 28.3.

IR: 2924 (w), 2364 (w), 1750 (m), 1557 (s), 1447 (m), 1308 (m), 1240 (m), 1147 (s), 1087 (m), 741 (m), 688 (s).

HRMS: (ESI) calcd for $C_{13}H_{15}NNaO_6S^+$ $[M+Na]^+$ 336.0512; found 336.0514.

$[\alpha]_D^{26}$= + 5 (*c* 1.48, $CHCl_3$)



Procedure: To a solution of selenone **5k** (85 mg, 0.20 mmol, 1 equiv) in MeOH (2 mL) was added PtO_2 (9 mg, 0.04 mmol, 0.2 equiv). The resulting mixture was stirred under H_2 atmosphere at room temperature for 16 hours. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 61 mg, 78% yield, Eluent: AcOEt/PE, 10:90 to 30:70

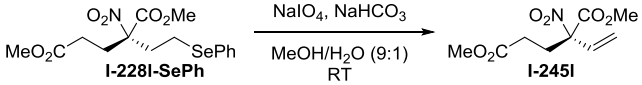
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.54 – 7.45 (m, 2H), 7.32 – 7.27 (m, 3H), 3.78 (s, 3H), 3.67 (s, 3H), 2.81 – 2.70 (m, 2H), 2.60 – 2.45 (m, 4H), 2.33 – 2.22 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 171.7, 166.1, 132.9, 129.2, 128.4, 127.4, 94.7, 53.5, 51.9, 35.7, 29.1, 28.3, 20.0.

IR: 2955 (w), 1739 (s), 1551 (s), 1437 (m), 1255 (m), 1201 (m), 739 (m), 692 (m).

HRMS: (ESI) calcd for $C_{15}H_{19}NNaO_6Se$ [M+Na] 412.0275; found 412.0279.



Procedure: To a solution of selenide **13k** (39 mg, 0.1 mmol, 1 equiv) in MeOH/H_2O (9:1, 0.9 mL of MeOH + 0.1 mL of H_2O) was added $NaHCO_3$ (13 mg, 0.15 mmol, 1.5 equiv) and $NaIO_4$ (24 mg, 0.11 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 14 mg, 61% yield, Eluent: AcOEt/PE, 10:90 to 30:70

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.38 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.56 (d, *J* = 11.1 Hz, 1H), 5.41 (d, *J* = 17.6 Hz, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 2.76 – 2.65 (m, 2H), 2.48 – 2.31 (m, 2H).

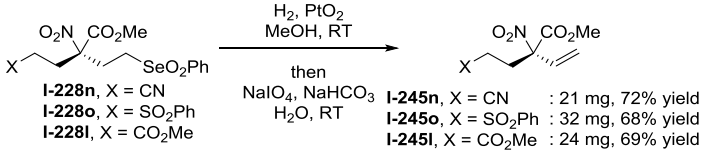
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 172.2, 166.1, 130.8, 120.7, 95.1, 54.0, 52.2, 30.4, 28.7.

IR: 2957 (w), 2361 (w), 1739 (s), 1438 (m), 1253 (s), 1202 (m), 983 (w).

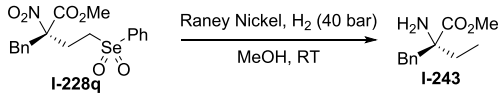
HRMS: (ESI) calcd for $C_9H_{13}NNaO_6^+$ $[M+Na]^+$ 254.0635; found 254.0635.

$[\alpha]_D^{26}$= + 6 (*c* 0.27, $CHCl_3$)

<u>One pot conversion of **5** to **14**:</u>



Procedure: To a solution of selenone **5** (0.15 mmol, 1 equiv) in methanol was added added PtO_2 (68 mg, 0.3 mmol, 0.2 equiv). The reaction mixture was stirred under H_2 atmosphere at room temperature for 16 hours. $NaHCO_3$ (19 mg, 0.23 mmol, 1.5 equiv), $NaIO_4$ (36mg, 0.17 mmol, 1.1 equiv) and water (0.1 mL) were then added. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.



Procedure: To a solution of selenone **5m** (35 mg, 0.082 mmol, 1equiv) in MeOH (1 mL) was added a suspension of Raney Nickel (0.5 mL) in H_2O. The resulting mixture was stirred in an autoclave under 40 bar of H_2 at room temperature for 16 hours. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 17mg, 68% yield, Eluent: AcOEt/PE 30:70

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): 7.32 – 7.21 (m, 3H), 7.17 – 7.10 (m, 2H), 3.71 (s, 3H), 3.18 (d, *J* = 13.2 Hz, 1H), 2.76 (d, *J* = 13.2 Hz, 1H), 2.02 – 1.89 (m, 1H), 1.77 – 1.67 (br s., 2H), 1.68 – 1.58 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H).

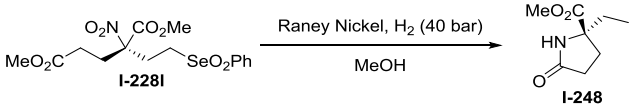
^{13}C NMR (100.62 MHz, $CDCl_3$): 177.1, 136.6, 130.0, 128.5, 127.1, 62.8, 52.1, 46.0, 33.4, 8.6.

IR: 2930 (w), 2359 (w), 1733 (s), 1456 (w), 1237 (m), 1197 (m), 867 (w), 742 (w), 703 (s).

HRMS: (ESI) calcd for $C_{12}H_{18}NO_2^+$ $[M+H]^+$ 208.1332; found 208.1339.

$[\alpha]_D^{26}$= + 4 (*c* 0.42, $CHCl_3$)

Synthesis of γ,γ-disubstituted γ-lactams **16k** and **17k**:



Procedure: To a solution of **5k** (95 mg, 0.23 mmol, 1equiv) in MeOH (2.3 mL) was added a suspension of Raney Nickel in H_2O (0.5 mL). The resulting mixture was stirred in an autoclave under 40 bar of H_2 at room temperature for 16 hours. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 23 mg, 59% yield, Eluent: AcOEt/PE, 60:40 to 80:20

Aspect: yellow oil

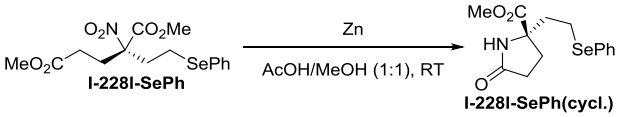
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 5.97 (s, 1H), 3.76 (s, 3H), 2.49 (ddd, *J* = 12.7, 9.1, 6.5 Hz, 1H), 2.41 – 2.35 (m, 2H), 2.15 – 2.02 (m, 1H), 1.94 – 1.84 (m, 1H), 1.81 – 1.72 (m, 1H), 0.90 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 176.9, 174.1, 66.2, 52.8, 32.4, 30.2, 29.8, 8.5.

IR: 2954 (w), 1737 (m), 1701 (s), 1436 (w), 1253 (w), 1163 (w).

HRMS: (ESI) calcd for $C_8H_{14}NO_3^+$ $[M+H]^+$ 172.0968; found 172.0969.

$[\alpha]_D^{26}$= - 15 (*c* 0.02, $CHCl_3$)



Procedure: To a solution of **13k** (106 mg, 0.27 mmol, 1 equiv) in AcOH/MeOH (1:1, 1.5 mL of AcOH + 1.5 mL of MeOH) was added zinc powder (353 mg, 5.4 mmol, 20 equiv). The reaction mixture was stirred at 50 °C for 16 hours. The reaction mixture was cooled down to room temperature, diluted with water and extracted with DCM (3 times). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 84 mg, 95%

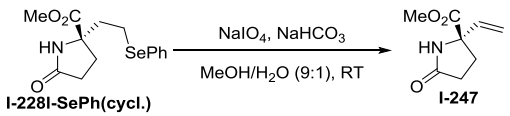
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.52 – 7.43 (m, 2H), 7.31 – 7.24 (m, 3H), 6.77 (s, 1H), 3.74 (s, 3H), 2.83 – 2.74 (m, 2H), 2.49 – 2.39 (m, 1H), 2.39 – 2.32 (m, 2H), 2.31 – 2.21 (m, 1H), 2.14 – 2.08 (m, 1H), 2.06 – 1.99 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 177.3, 173.5, 133.0, 129.4, 129.3, 127.5, 66.1, 53.0, 39.8, 30.8, 29.6, 21.2.

IR: 2953 (w), 1734 (m), 1696 (s), 1435 (w), 1258 (m), 1197 (m), 1167 (m), 737 (m), 692 (m).

HRMS: (ESI) calcd for $C_{14}H_{18}NO_3Se^+$ $[M+H]^+$ 328.0446; found 328.0442.



Procedure: To a solution of selenide **S1** (75 mg, 0.23 mmol, 1 equiv) in MeOH/H_2O (9:1, 1.8 mL of MeOH + 0.2 mL of H_2O) was added $NaHCO_3$ (29 mg, 0.35 mmol, 1.5 equiv) and $NaIO_4$ (53 mg, 0.25 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

Yield: 25 mg, 63% yield Eluent: AcOEt/PE, 60:40 to 80:20

Aspect: yellow oil

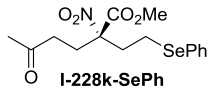
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.21 (s, 1H), 6.07 (dd, *J* = 17.2, 10.5 Hz, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.25 (d, *J* = 10.5 Hz, 1H), 3.78 (s, 3H), 2.63 – 2.47 (m, 1H), 2.41 – 2.31 (m, 2H), 2.23 – 2.12 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 177.0, 172.5, 137.3, 115.3, 66.9, 53.1, 32.3, 29.2.

IR: 2925 (s), 1739 (s), 1710 (s), 1462 (w), 1439 (w), 1263 (w), 1164 (w).

HRMS: (ESI) calcd for $C_8H_{12}NO_3^+$ $[M+H]^+$ 170.0812; found 170.0811.

$[\alpha]_D^{26}$= -8 (*c* 0.05, $CHCl_3$)



I-228k-SePh

Procedure: To a solution of PtO_2 (0.1 equiv) in MeOH was added methyl 2-nitro-2-(2-(phenylselenonyl)ethyl)hexanoate (**33e**) (1 equiv). The resulting mixture was stirred under H_2 atmosphere until complete consumption of the starting material (TLC monitoring, around 2 hours). The reaction mixture was filtered through a Celite pad and concentrated under reduced pressure. The crude product was used without further purification.

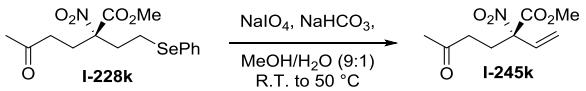
Yield: quantitative

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.53 – 7.45 (m, 2H), 7.33 – 7.26 (m, 3H), 3.77 (s, 3H), 2.85 – 2.63 (m, 2H), 2.59 – 2.48 (m, 2H), 2.46 – 2.37 (m, 4H), 2.11 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 205.6, 166.6, 133.4, 129.5, 128.8, 127.8, 95.2, 53.7, 37.7, 36.4, 30.1, 28.1, 20.4.

IR: 2955 (w), 1750 (m), 1719 (m), 1551, (s), 1438 (m), 1357 (w), 1256 (w), 740 (m), 692 (w).

HRMS: (ESI) calcd for $C_{15}H_{19}NO_5SeNa$+ [M+Na]+ 396.0321; found 396.0325.



I-228k **I-245k**

Procedure: To a solution of $NaIO_4$ and $NaHCO_3$ in MeOH/H_2O (9:1) was added the selenide **XX** (). The reaction mixture was stirred 2 hours at room temperature and heated to 50 °C during 12 hours. The reaction mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.

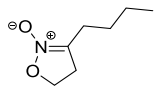
Yield: 95%, Eluent: AcOEt/PE 10:90 to 20:80

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.36 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.54 (d, *J* = 11.0 Hz, 1H), 5.38 (d, *J* = 17.6 Hz, 1H), 3.83 (s, 3H), 2.69 – 2.58 (m, 2H), 2.56 – 2.48 (m, 2H), 2.15 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 205.8, 166.2, 131.2, 120.5, 95.4, 53.9, 37.9, 30.1, 28.9.

IR: 2922 (w), 2853 (m), 1751 (m), 1718 (m), 1554 (s), 1252 (m), 1170 (w).

HRMS: (ESI) calcd for $C_9H_{13}NO_5Na+$ [M+Na]+ 238.0686; found 238.0690.



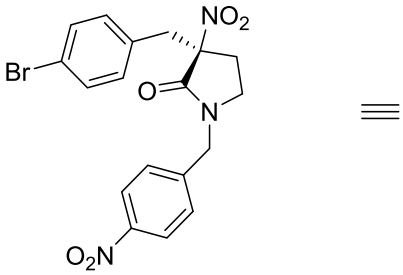
I-259

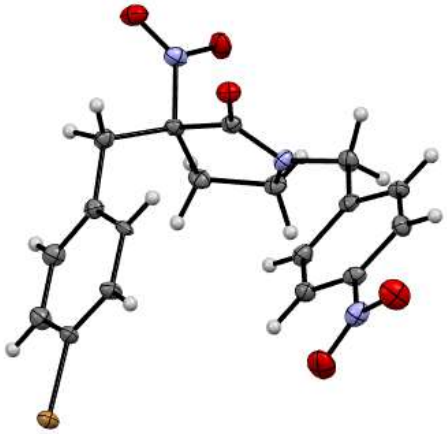
^{1}H NMR (400.13 MHz, $CDCl_3$): 4.41 (t, *J* = 8.7 Hz, 2H), 3.17 – 2.98 (m, 2H), 2.45 – 2.35 (m, 2H), 1.58 – 1.47 (m, 2H), 1.44 – 1.32 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): 115.8, 63.2, 33.2, 27.7, 26.0, 22.6, 13.8.

IR: 2959 (w), 2930 (w), 2873 (w), 1639 (s), 1466 (w), 1381 (w), 1269 (w), 1186 (w), 1088 (w), 863 (w).

Crystallographic data of compound 7





Summary of Data CCDC 1496191

Compound Name: (S)-3-(4-bromobenzyl)-3-nitro-1-(4-nitrobenzyl)pyrrolidin-2-one

Formula: C18 H16 Br1 N3 O5

Unit Cell Parameters: a 13.044(3) b 9.5725(6) c 14.578(3) Ia

Check cif of CCDC 1496191

Bond precision: C-C = 0.0052 A Wavelength=0.71073

Cell: a=13.044(3) b=9.5725(6) c=14.578(3)
alpha=90 beta=104.884(10) gamma=90
Temperature: 100 K

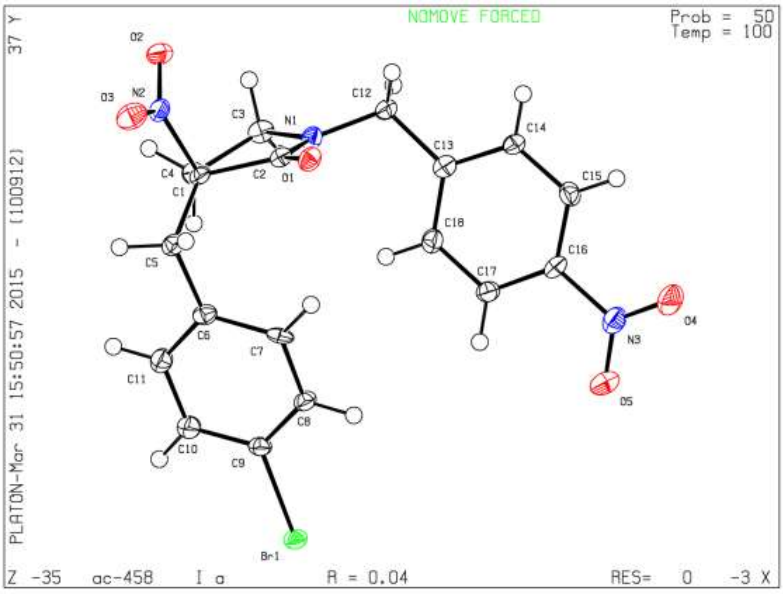
	Calculated	Reported
Volume	1759.2(6)	1759.2(6)
Space group	I a	I a
Hall group	I -2ya	I -2ya
Moiety formula	C18 H16 Br N3 O5	C18 H16 Br N3 O5
Sum formula	C18 H16 Br N3 O5	C18 H16 Br N3 O5
Mr	434.24	434.25
Dx,g cm-3	1.640	1.640
Z	4	4
Mu (mm-1)	2.373	2.373
F000	880.0	880.0
F000'	879.26	
h,k,lmax	18,13,21	18,13,21
Nref	5602[2804]	5195
Tmin,Tmax	0.418,0.527	0.482,0.733
Tmin'	0.323	

Correction method= # Reported T Limits: Tmin=0.482 Tmax=0.733
AbsCorr = MULTI-SCAN

Data completeness= 1.85/0.93 Theta(max)= 30.990

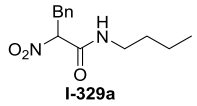
R(reflections)= 0.0420(4893) wR2(reflections)= 0.1089(5195)

S = 1.102 Npar= 245



Chapter 2

Characterization data



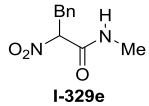
I-329a

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.35 – 7.27 (m, 3H), 7.22 – 7.18 (m, 2H), 6.14 (s, 1H), 5.20 (dd, *J* = 8.2, 6.8 Hz, 1H), 3.56 – 3.46 (m, 2H), 3.34 – 3.20 (m, 2H), 1.52 – 1.40 (m, 2H), 1.34 – 1.23 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 162.6, 134.4, 129.1, 127.9, 91.1, 40.1, 37.4, 31.3, 20.0, 13.8.

IR: 3299 (w), 2954 (w), 2934 (w), 2864 (w), 1666 (s), 1553 (s), 752 (w), 701 (w).

HRMS: (ESI) calcd for $C_{13}H_{18}N_2NaO_3^+$ $[M+Na]^+$ 273.1210; found 273.1214.



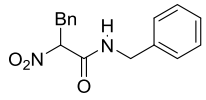
I-329e

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.44 – 7.26 (m, 4H), 7.23 – 7.09 (m, 2H), 6.24 (s, 1H), 5.22 (dd, *J* = 8.0, 6.9 Hz, 1H), 3.51 (d, *J* = 7.5 Hz, 2H), 2.86 (d, *J* = 4.8 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 163.3, 134.4, 129.1, 129.0, 128.0, 91.1, 37.4, 27.0.

IR: 3302 (w), 1667 (s), 1553 (s), 1414 (w), 1374 (w), 759 (w), 700 (m).

HRMS: (ESI) calcd for $C_{10}H_{12}N_2NaO_3^+$ $[M+Na]^+$ 231.0740; found 231.0748.

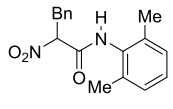


I-329d

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, 6H), 7.23 – 7.12 (m, 4H), 6.42 (s, 1H), 5.24 (dd, *J* = 8.1, 6.9 Hz, 1H), 4.45 (d, *J* = 5.6 Hz, 2H), 3.66 – 3.37 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 162.6, 136.7, 134.2, 129.2, 129.1, 129.0, 128.1, 128.0, 127.9, 91.0, 44.3, 37.3.**IR:** 3288 (w), 3063 (w), 1665 (s), 1553 (s), 1456 (w), 1360 (w), 1240 (w), 748 (m), 736 (w), 698 (s).

HRMS: (ESI) calcd for $C_{16}H_{16}N_2NaO_3^+$ $[M+Na]^+$ 307.1053; found 307.1054.



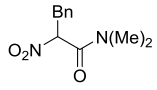
I-329c

^{1}H NMR (400.13 MHz, Methanol-d_4) δ 7.39 – 7.33 (m, 4H), 7.33 – 7.25 (m, 1H), 7.12 – 7.05 (m, 1H), 7.04 – 6.94 (m, 2H), 5.71 (dd, *J* = 9.6, 6.1 Hz, 1H), 4.86 (s, 6H), 3.64 (dd, *J* = 13.5, 6.1 Hz, 1H), 3.51 (dd, *J* = 13.6, 9.7 Hz, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 164.2, 136.8, 135.8, 134.3, 130.7, 129.9, 129.1, 128.8, 128.6, 89.8, 36.7, 18.0.

IR: 2359 (s), 2335 (m), 1666 (m), 1558 (s), 767 (w), 703 (w).

HRMS: (ESI) calcd for $C_{17}H_{17}N_2O_3$ [M+H-1] 297.1239; found 297.1239.



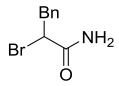
I-335

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.32 – 7.28 (m, 2H), 7.27 – 7.22 (m, 3H), 4.60 (dd, *J* = 8.0, 6.7 Hz, 1H), 3.59 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.26 (dd, *J* = 14.0, 6.6 Hz, 1H), 2.96 (s, 3H), 2.95 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.4, 137.9, 129.6, 128.7, 127.2, 43.7, 41.2, 37.6, 36.5.

IR: 2926 (w), 1656 (s), 1557 (m), 1496 (w), 1404 (w), 1361 (w), 1259 (w), 1138 (w), 750 (w), 702 (w).

HRMS: (ESI) calcd for $C_{11}H_{15}N_2O_3^+$ $[M+H]^+$ 223.1077; found 223.1078.



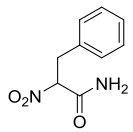
I-328-Br

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.41 – 7.29 (m, 2H), 7.27 – 7.22 (m, 3H), 6.16 (s, 1H), 5.71 (s, 1H), 4.47 (dd, *J* = 7.9, 5.7 Hz, 1H), 3.55 (dd, *J* = 14.4, 5.7 Hz, 1H), 3.26 (dd, *J* = 14.4, 7.9 Hz, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.6, 137.0, 129.6, 128.7, 127.4, 50.5, 41.7.

IR: 3436 (w), 3301 (w), 3196 (w), 1674 (s), 1607 (m), 1411 (w), 1207 (w), 1045 (w), 745 (w), 700 (s).

HRMS: (ESI) calcd for C9H10BrNNaO+ [M+Na]+ 249.9838; found 249.9840.



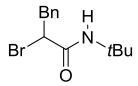
I-328

^{1}H NMR (400.13 MHz, CD_3OD): δ 7.32 – 7.05 (m, 5H), 5.37 (dd, *J* = 8.4, 6.9 Hz, 1H), 3.47 – 3.37 (m, 1H), 3.32 – 3.23 (m, 1H).

^{13}C NMR (100.62 MHz, CD_3OD): δ 166.5, 134.9, 128.8, 128.3, 127.0, 89.2, 35.7.

IR: 3435 (w), 3311 (w), 3201 (w), 1701 (s), 1619 (w), 1542 (s), 1416 (w), 1242 (w), 749 (w), 702 (m).

HRMS: (ESI) calcd for $C_{11}H_{11}NNaO_4^+$ $[M+Na]^+$ 244.0580; found 244.0581.

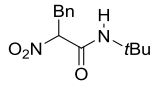


I-329b-Br

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.51 – 7.39 (m, 2H), 7.39 – 7.28 (m, 3H), 6.49 (s, 1H), 5.33 (s, 1H), 1.40 (s, 9H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.1, 138.1, 129.1, 128.4, 52.3, 28.6.

IR: 3297 (w), 2980 (w), 1656 (s), 1639 (m), 1556 (m), 1452 (w), 1364 (w), 1259 (w), 1223 (w), 714 (w).



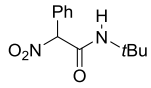
I-329b

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 3H), 7.25 – 7.14 (m, 2H), 5.87 (s, 1H), 5.09 (dd, *J* = 7.9, 7.1 Hz, 1H), 3.53 – 3.39 (m, 2H), 1.31 (s, 9H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 161.5, 134.5, 129.2, 129.1, 127.9, 91.5, 52.6, 37.2, 28.4.

IR: 3324 (w), 2973 (w), 1669 (s), 1557 (s), 1367 (m), 1222 (m), 752 (m), 699 (m).

HRMS: (ESI) calcd for C13H18N2NaO3+ [M+Na]+ 273.1210; found 273.1210.



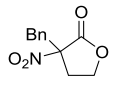
I-329b-Ph

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.54 – 7.38 (m, 5H), 6.09 (s, 1H), 5.98 (s, 1H), 1.36 (s, 9H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 161.9, 130.8, 130.4, 129.6, 129.5, 129.3, 128.0, 93.2, 52.8, 28.5.

IR: 3323 (w), 2973 (w), 1671 (m), 1561 (s), 1457 (w), 1368 (m), 1222 (w), 704 (w).

HRMS: (ESI) calcd for $C_{12}H_{17}N_2O_3^+$ $[M+H]^+$ 237.1234; found 237.1232.



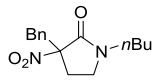
I-336

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.41 – 7.31 (m, 3H), 7.25 – 7.19 (m, 2H), 4.46 – 4.32 (m, 1H), 3.94 (td, *J* = 8.8, 4.0 Hz, 1H), 3.69 – 3.59 (m, 2H), 2.94 (ddd, *J* = 14.6, 7.5, 4.0 Hz, 1H), 2.59 (ddd, *J* = 14.5, 8.5, 7.7 Hz, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 169.1, 132.3, 130.3, 129.4, 128.5, 92.0, 66.0, 39.5, 31.8.

IR: 1781 (s), 1552 (s), 1456 (w), 1349 (w), 1222 (w), 1174 (m), 1151 (w), 1023 (m), 702 (s).

HRMS: (ESI) calcd for $C_{11}H_{11}NNaO_4^+$ $[M+Na]^+$ 244.0580; found 244.0581.



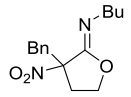
I-337

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 3H), 7.24 – 7.20 (m, 2H), 3.65 (d, *J* = 13.7 Hz, 1H), 3.50 (d, *J* = 13.7 Hz, 1H), 3.44 (ddd, *J* = 9.6, 8.1, 6.1 Hz, 1H), 3.36 – 3.15 (m, 2H), 2.81 (ddd, *J* = 9.6, 8.6, 3.7 Hz, 1H), 2.70 (ddd, *J* = 14.4, 8.1, 3.7 Hz, 1H), 2.34 (ddd, *J* = 14.6, 8.6, 6.1 Hz, 1H), 1.49 – 1.35 (m, 2H), 1.28 – 1.13 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.4, 133.6, 130.5, 128.9, 127.8, 94.6, 44.2, 43.4, 39.4, 28.9, 28.4, 19.9, 13.8.

IR: 2959 (w), 2932 (w), 2869 (w), 1705 (s), 1545 (s), 1456 (w), 1275 (w), 702 (w).

HRMS: (ESI) calcd for $C_{15}H_{20}N_2NaO_3^+$ $[M+Na]^+$ 299.1366; found 299.1375.



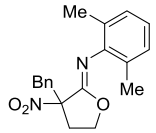
I-339-Bu-imidate

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 3H), 7.25 – 7.19 (m, 2H), 4.35 – 4.25 (m, 1H), 4.11 – 3.98 (m, 1H), 3.73 (d, *J* = 14.0 Hz, 1H), 3.50 (d, *J* = 14.0 Hz, 1H), 3.42 – 3.31 (m, 2H), 2.89 – 2.70 (m, 1H), 2.51 – 2.34 (m, 1H), 1.70 – 1.54 (m, 2H), 1.47 – 1.30 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 156.8, 134.2, 130.5, 128.8, 127.9, 93.8, 67.4, 47.8, 40.6, 33.1, 32.5, 20.8, 14.1.

IR: 2958 (w), 2932 (w), 2872 (w), 1710 (s), 1550 (s), 1351 (w), 1181 (w), 1030 (m), 703 (w).

HRMS: (ESI) calcd for $C_{15}H_{21}N_2O_3^+$ $[M+H]^+$ 277.1547; found 277.1547.



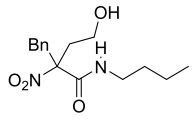
I-339-Xyl-imidate

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.37 – 7.29 (m, 5H), 7.06 – 6.97 (m, 2H), 6.97 – 6.83 (m, 1H), 4.38 (td, *J* = 9.3, 6.3 Hz, 1H), 4.27 (td, *J* = 8.7, 2.1 Hz, 1H), 4.16 (d, *J* = 14.6 Hz, 1H), 3.44 (d, *J* = 14.6 Hz, 1H), 2.94 (ddd, *J* = 14.6, 6.3, 2.2 Hz, 1H), 2.56 (ddd, *J* = 14.5, 9.8, 8.7 Hz, 1H), 2.08 (s, 6H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 155.8, 143.6, 133.9, 130.4, 129.0, 128.1, 128.0, 127.9, 124.0, 94.3, 68.4, 41.1, 33.2, 18.1.

IR: 2921 (w), 2363 (w), 1715 (s), 1551 (s), 1472 (w), 1213 (w), 1182 (w), 1027 (m), 768 (w), 703 (w).

HRMS: (ESI) calcd for $C_{19}H_{21}N_2O_3^+$ $[M+H]^+$ 325.1547; found 325.1547.



I-339

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.33 – 7.24 (m, 3H), 7.17 – 7.04 (m, 2H), 6.96 (s, 1H), 3.83 – 3.70 (m, 2H), 3.63 (d, *J* = 13.9 Hz, 1H), 3.48 (d, *J* = 13.9 Hz, 1H), 3.33 – 3.20 (m, 2H), 2.50 (t, *J* = 6.0 Hz, 2H), 1.88 (s, 1H), 1.54 – 1.35 (m, 2H), 1.35 – 1.17 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.1, 133.3, 130.1, 128.8, 128.1, 97.5, 58.7, 44.3, 40.2, 38.5, 31.1, 20.1, 13.8.

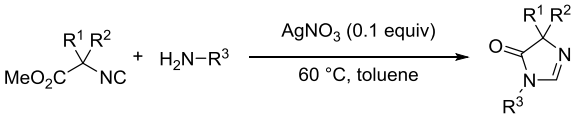
IR: 3362 (w), 2959 (w), 2932 (w), 2868 (w), 1659 (m), 1548 (s), 1457 (w), 1048 (w), 743 (w), 703 (w).

HRMS: (ESI) calcd for $C_{12}H_{19}NNaO_2^+$ $[M+Na]^+$ 232.1308; found 232.1314.

Part II

Chapter 3

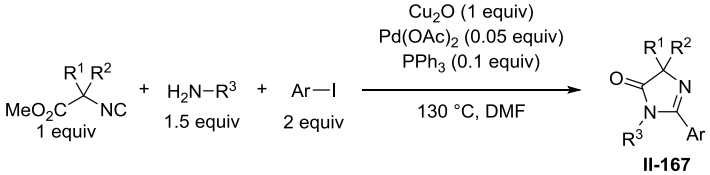
General procedures



II-123

General procedure A:

To a solution of α,α-disubstituted α-isocyanoacetate **X** (0.1 mmol, 1 equiv) and primary amine **X** (0.12 mmol, 1.2 equiv) in toluene (1 mL) was added $AgNO_3$ (0.01 mmol, 0.1 equiv)**.** The reaction mixture was stirred at 60 °C until complete consumption of the starting material (TLC monitoring, around 12 hours). The reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the pure product.

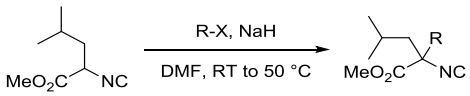


II-167

General procedure B:

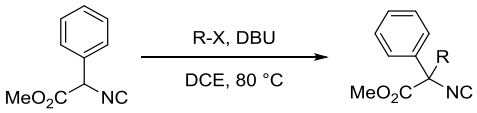
To a solution of α,α-disubstituted α-isocyanoacetate **X** (0.1 mmol, 1 equiv), primary amine **X** (0.15 mmol, 1.5 equiv), aryl iodide (0.2 mmol, 2 equiv) and PPh_3 (0.01 mmol, 0.1 mmol) in DMF (1 mL) were added $Pd(OAc)_2$ (0.005 mmol, 0.05 equiv) and Cu_2O (0.1 mmol, 1 equiv). The reaction was performed in a sealed tube under

inert atmosphere**.** The reaction mixture was stirred at 130 °C for 12h. The reaction mixture was cooled down to room temperature, diluted with AcOEt (10 mL), washed with a 1:1 mixture of aqueous ammonia and brine (2 times) and brine only (3 times). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the pure product.



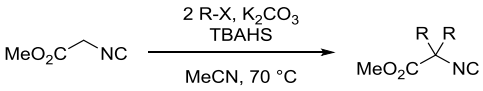
General procedure C:

To a solution of methyl α-isopropyl α-isocyanoacetate (1 equiv) in DMF (0.1 M) was added portion-wise NaH (1.5 equiv), After 30 minutes, the corresponding alkyl halide (1.5 equiv) was added drop-wise. The reaction mixture was stirred at 50 °C for 12 hours. The reaction mixture was cooled to room temperature, quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with DCM (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.



General procedure D:

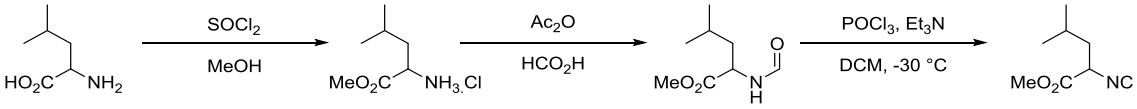
To a solution of methyl α-phenyl α-isocyanoacetate (1 equiv) in DCE (0.1 M) were added DBU (1.1 equiv) and the corresponding alkyl halide (1.5 equiv). The reaction mixture was stirred at 80 °C for 12 hours. The reaction mixture was cooled to room temperature, quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with DCM (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.



General procedure E, following the literature report[215]:

To a solution of methyl α-isocyanoacetate (1 equiv) in MeCN (0.1 M) were added K_2CO_3 (4.4 equiv), TBAHS (0.1 equiv.) and the corresponding alkyl halide (2 equiv). The reaction mixture was stirred at 70 °C for 12 hours. The reaction mixture was cooled to room temperature, quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with DCM (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

haracterisation data

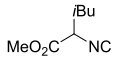


To a solution of leucine in methanol was added $SOCl_2$. The reaction mixture was stirred at RT for 2 hours and evaporated to dryness to give the corresponding methyl ester hydrochloride which was washed with NaOH (3M) and extraceted with DCM (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting amine was directly used without further purification.

To a solution formic acid (100 equiv) was added Ac_2O (10 equiv). The reaction mixture was stirred at 60 °C for 1 hour. After cooling down the reaction mixture the ammonium salt was added. The reaction mixture was stirred at RT for 2 hour and evaporated to dryness to give the corresponding formamide which was directly used without further purification.

To a solution of formamide in DCM (0.3 M) was added triethylamine (2.7 equiv). The reaction mixture was cooled to -30 °C. $POCl_3$ (1.2 equiv) was added and the solution was stirred at -30 °C with TLC monitoring (around 3h). The reaction mixture was cooled to room temperature, quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with DCM (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Eluent: PE/AcOEt: 9/1 to 7/3) to afford the desire isocyanoacetate.

Characterization data



Yield: 30% yield over three steps

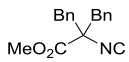
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 4.29 (dd, *J* = 10.0, 4.6 Hz, 1H), 3.82 (s, 2H), 2.02 – 1.77 (m, 2H), 1.73 – 1.55 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 167.8, 160.1, 55.2 (t, *J* = 7.0 Hz), 53.5, 41.4, 24.9, 22.7, 21.0.

IR: 2960 (w), 2148 (m), 1756 (s), 1439 (w), 1274 (m), 1235 (m), 1207 (m), 1142 (w), 1011 (w).

HRMS: (ESI) calcd for $C_8H_{14}NO_2^+$ $[M+H]^+$ 156.1019; found 156.1021.

α,α-disubstituted α-isocyanoacetate



From literature report[215]

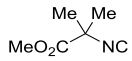
Aspect: white solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.37 – 7.30 (m, 6H), 7.29 – 7.25 (m, 4H), 3.59 (s, 3H), 3.38 (d, *J* = 13.5 Hz, 2H), 3.07 (d, *J* = 13.5 Hz, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.6, 161.4, 133.6, 130.3, 128.6, 128.1, 70.6, 53.3, 45.0.

IR: 3030 (w), 2142 (w), 1740 (m), 1497 (w), 1441 (w), 1236 (m), 1208 (m), 1088 (m), 1036 (w), 958 (w), 748 (m), 701 (s).

HRMS: (ESI) calcd for $C_{18}H_{18}NO_2^+$ $[M+H]^+$ 280.1332; found 280.1339.



From literature report [216]

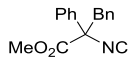
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.83 (s, 3H), 1.67 (s, 6H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.2, 158.0, 59.7 (t, *J* = 6 Hz), 53.7, 27.7.

IR: 2958 (w), 2141 (w), 1748 (s), 1437 (w), 1284 (m), 1193 (m), 1153 (s), 992 (w), 864 (w), 783 (w), 767 (w).

HRMS: (ESI) calcd for $C_6H_{10}NO_2^+$ $[M+H]^+$ 128.0706; found 128.0705.



General procedure D

Yield: 76% yield (with benzyl bromide)

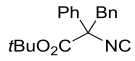
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.63 – 7.53 (m, 2H), 7.47 – 7.37 (m, 3H), 7.30 – 7.24 (m, 3H), 7.17 – 7.08 (m, 2H), 3.77 (s, 3H), 3.73 (d, *J* = 13.7 Hz, 1H), 3.33 (d, *J* = 13.7 Hz, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.1, 162.2, 135.1, 133.6, 130.7, 129.2, 129.0, 128.4, 127.9, 125.4, 72.0, 54.0, 46.0.

IR: 2138 (w), 1746 (m), 1498 (w), 1436 (w), 1260 (m), 1035 (w), 732 (m), 697 (s).

HRMS: (ESI) calcd for $C_{17}H_{15}NNaO_2^+$ $[M+Na]^+$ 288.0995; found 288.0996.



General procedure D

Aspect: yellow oil

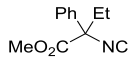
Yield: 82% yield (with benzyl bromide)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.60 – 7.55 (m, 2H), 7.47 – 7.34 (m, 3H), 7.30 – 7.23 (m, 3H), 7.21 – 7.13 (m, 2H), 3.70 (d, *J* = 13.7 Hz, 1H), 3.29 (d, *J* = 13.8 Hz, 1H), 1.41 (s, 9H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.3, 161.3, 135.7, 134.0, 130.8, 128.9, 128.8, 128.2, 127.7, 125.4, 84.4, 72.3, 45.7, 27.7.

IR: 2980 (w), 2137 (w), 1735 (m), 1497 (w), 1450 (w), 1371 (w), 1262 (m), 1259 (m), 1150 (s), 839 (m), 738 (m), 697 (s).

HRMS: (ESI) calcd for $C_{20}H_{21}NNaO_2^+$ $[M+Na]^+$ 330.1464; found 330.1472.



General procedure D

Aspect: yellow oil

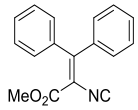
Yield: 76% yield (with ethyl iodide)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.63 – 7.51 (m, 2H), 7.48 – 7.33 (m, 3H), 3.78 (s, 3H), 2.44 (dq, *J* = 14.3, 7.1 Hz, 1H), 2.19 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.02 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.5, 160.9, 135.2, 129.0, 129.0, 125.3, 71.9, 53.9, 33.5, 8.7.

IR: 2138 (m), 1747 (s), 1450 (w), 1242 (s), 1139 (w), 1011 (w), 759 (w), 731 (m), 696 (s), 613 (w).

HRMS: (ESI) calcd for $C_{12}H_{13}NO_2$ [M+] 203.0941; found 203.0940.



From literature report [217]

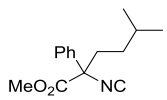
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.50 – 7.30 (m, 8H), 7.21 – 7.08 (m, 2H), 3.68 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 169.7, 162.3, 154.6, 137.8, 137.4, 130.3, 129.9, 129.6, 129.1, 128.4, 128.2, 113.7, 52.9.

IR: 2113 (w), 1729 (m), 1697 (w), 1445 (w), 1332 (w), 1255 (m), 1115 (m), 765 (w), 747 (w), 699 (s).

HRMS: (ESI) calcd for $C_{17}H_{14}NO_2^+$ $[M+H]^+$ 264.1019; found 264.1025.



General procedure D

Aspect: yellow oil

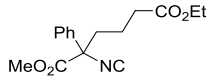
Yield: 72% yield (with 1-bromo-3-methylbutane)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.61 – 7.52 (m, 2H), 7.45 – 7.33 (m, 3H), 3.78 (s, 3H), 2.45 – 2.31 (ddd, *J* = 6.3, 10.5, 13.8 Hz, 1H), 2.23 – 2.09 (ddd, *J* = 6.3, 10.5, 13.8 Hz, 1H), 1.65 – 1.49 (m, 1H), 1.36 – 1.20 (m, 2H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.6, 160.8, 135.4, 129.0, 129.0, 125.2, 71.3, 53.9, 38.1, 33.1, 27.9, 22.6, 22.4.

IR: 2957 (w), 2872 (w), 2136 (m), 1748 (s), 1450 (w), 1436 (w), 1252 (s), 1144 (w), 1025 (w), 775 (w), 732 (m), 697 (s).

HRMS: (ESI) calcd for $C_{15}H_{20}NO_2^+$ $[M+H]^+$ 246.1489; found 246.1494.



General procedure D

Aspect: yellow oil

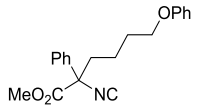
Yield: 74% yield (with ethyl 4-iodobutanoate)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.59 – 7.51 (m, 2H), 7.44 – 7.35 (m, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.47 – 2.39 (m, 1H), 2.38 – 2.32 (m, 2H), 2.29 – 2.19 (m, 1H), 1.80 – 1.66 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 172.6, 168.2, 161.5, 134.8, 129.1, 129.0, 125.1, 70.8, 60.5, 54.0, 39.0, 33.4, 19.7, 14.3.

IR: 2981 (w), 2136 (m), 1731 (s), 1450 (w), 1249 (s), 1186 (s), 1097 (m), 1032 (w), 772 (w), 732 (m), 697 (s).

HRMS: (ESI) calcd for $C_{16}H_{19}NNaO_4^+$ $[M+Na]^+$ 312.1206; found 312.1211.



General procedure D

Aspect: yellow oil

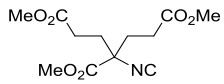
Yield: 81% yield (with (4-bromobutoxy)benzene)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.60 – 7.52 (m, 2H), 7.47 – 7.36 (m, 3H), 7.32 – 7.24 (m, 2H), 6.98 – 6.91 (m, 1H), 6.89 – 6.84 (m, 2H), 3.95 (t, *J* = 6.3 Hz, 2H), 3.78 (s, 3H), 2.55 – 2.39 (m, 1H), 2.29 – 2.20 (m, 1H), 1.94 – 1.75 (m, 2H), 1.68 – 1.52 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.4, 161.3, 159.0, 135.2, 129.6, 129.1, 129.1, 125.2, 120.8, 114.6, 71.1, 67.3, 54.0, 39.7, 28.8, 21.2.

IR: 2952 (w), 2136 (w), 1747 (m), 1599 (w), 1496 (m), 1243 (s), 1173 (m), 1034 (w), 754 (s), 731 (m), 693 (s).

HRMS: (ESI) calcd for $C_{20}H_{21}NNaO_3^+$ $[M+Na]^+$ 346.1414; found 346.1418.



General procedure E

Aspect: yellow oil

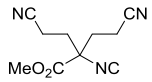
Yield: 65% yield (with methyl acrylate)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.65 (s, 6H), 2.60 – 2.47 (ddd, *J* = 5.4, 10.8, 17.2 Hz, 2H), 2.40 – 2.20 (m, 4H), 2.20 – 2.08 (ddd, *J* = 5.4, 10.8, 14.1 Hz, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 172.0, 168.1, 161.3, 66.7, 53.8, 52.0, 33.8, 29.0.

IR: 2956 (w), 2136 (w), 1735 (s), 1438 (m), 1200 (s), 1174 (s), 1094 (m), 975 (w), 915 (w), 816 (w), 733 (m).

HRMS: (ESI) calcd for $C_{12}H_{17}NNaO_6^+$ $[M+Na]^+$ 294.0948; found 294.0950.



General procedure E

Aspect: yellow oil

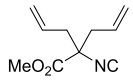
Yield: 60% yield (with acrylonitrile)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.93 (s, 3H), 2.70 – 2.59 (m, 2H), 2.56 – 2.44 (m, 2H), 2.48 – 2.38 (m, 2H), 2.26 – 2.14 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.4, 164.2, 117.1, 65.7, 54.5, 34.4, 12.8.

IR: 2960 (w), 2135 (m), 1733 (s), 1449 (m), 1375 (w), 1245 (s), 1219 (s), 1098 (m), 1046 (m), 737 (m).

HRMS: (ESI) calcd for $C_{10}H_{11}N_3NaO_2^+$ $[M+Na]^+$ 228.0743; found 228.0740.



General procedure E

Aspect: yellow oil

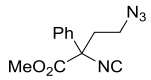
Yield: 77% yield (with allyl bromide)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 5.87 – 5.7 (ddt, 7.26, 7.26, 10.31, 16.91, 2H), 5.27 – 5.25 (m, 1H), 5.25 – 5.22 (m, 2H), 5.21 – 5.18 (m, 1H), 3.79 (s, 3H), 2.65 (dd, *J* = 14.0, 7.4 Hz, 2H), 2.55 (dd, *J* = 13.9, 7.1 Hz, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.4, 159.8, 129.9, 121.1, 67.8, 53.3, 42.6.

IR: 2956 (w), 2138 (m), 1748 (s), 1439 (m), 1222 (s), 1155 (m), 1030 (m), 994 (s), 928 (s), 669 (m).

HRMS: (ESI) calcd for $C_{10}H_{14}NO_2^+$ $[M+H]^+$ 180.1019; found 180.1020.



From literature report [218]

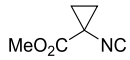
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.59 – 7.51 (m, 2H), 7.48 – 7.36 (m, 3H), 3.81 (s, 3H), 3.61 – 3.31 (m, 2H), 2.76 (ddd, *J* = 14.0, 8.5, 7.3 Hz, 1H), 2.40 (ddd, *J* = 14.0, 8.5, 4.8 Hz, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 167.7, 162.7, 134.5, 129.5, 129.3, 125.0, 68.9, 54.3, 47.0, 38.5.

IR: 2134 (m), 1748 (s), 1450 (w), 1436 (w), 1249 (s), 1214 (m), 1103 (w), 760 (w), 730 (m), 697 (s).

HRMS: (ESI) calcd for $C_{12}H_{12}N_4NaO_2^+$ $[M+Na]^+$ 267.0852; found 267.0857.



From literature report [219]

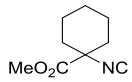
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.82 (s, 3H), 1.70 – 1.62 (m, 2H), 1.59 – 1.53 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.4, 158.0, 53.7, 34.7 (t, *J* = 12.0 Hz), 20.0.

IR: 2958 (w), 2363 (w), 2139 (w), 1742 (s), 1440 (m), 1332 (s), 1202 (s), 1163 (s).

HRMS: (ESI) calcd for $C_6H_8NO_2^+$ $[M+H]^+$ 126.0550; found 126.0549.



From literature report [219]

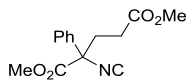
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.82 (s, 3H), 2.05 – 1.94 (m, 2H), 1.89 – 1.78 (m, 2H), 1.76 – 1.64 (m, 5H), 1.34 – 1.19 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.3, 158.8, 64.5, 53.6, 34.4, 24.5, 21.0.

IR: 2940 (w), 2864 (w), 2136 (m), 1746 (s), 1452 (w), 1437 (w), 1280 (s), 1245 (s), 1151 (m), 1069 (m).

HRMS: (ESI) calcd for $C_9H_{14}NO_2^+$ $[M+H]^+$ 168.1019; found 168.1019.



General procedure D

Aspect: yellow oil

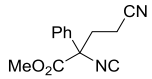
Yield: 85% yield (with methyl acrylate)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.58 – 7.47 (m, 2H), 7.47 – 7.33 (m, 3H), 3.78 (s, 3H), 3.65 (s, 3H), 2.78 – 2.66 (ddd, *J* = 5.0, 10.9, 13.7, 1H), 2.62 – 2.52 (ddd, 5.0, 10.9, 13.7 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.41 – 2.29 (ddd, *J* = 5.0, 10.9, 16.20 Hz, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 172.2, 167.8, 162.1, 134.3, 129.3, 129.2, 125.1, 70.1, 54.1, 52.0, 34.8, 29.3.

IR: 2955 (w), 2135 (m), 1738 (s), 1437 (m), 1249 (s), 1200 (m), 1176 (m), 1073 (w), 733 (m), 697 (m).

HRMS: (ESI) calcd for $C_{14}H_{15}NNaO_4^+$ $[M+Na]^+$ 284.0893; found 284.0892.



General procedure D

Aspect: yellow oil

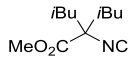
Yield: 82% yield (with acrylonitrile)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.56 – 7.49 (m, 2H), 7.48 – 7.39 (m, 3H), 3.81 (s, 3H), 2.82 – 2.71 (m, 1H), 2.65 – 2.47 (m, 2H), 2.44 – 2.30 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 167.0, 163.5, 133.2, 129.8, 129.5, 124.8, 117.7, 69.5, 54.4, 35.4, 12.9.

IR: 2957 (w), 2133 (m), 1748 (s), 1450 (m), 1253 (s), 1218 (m), 1089 (w), 1071 (m), 913 (w), 731 (s), 697 (s).

HRMS: (ESI) calcd for $C_{13}H_{12}N_2NaO_2^+$ $[M+Na]^+$ 251.0791; found 251.0792.



General procedure C

Aspect: yellow oil

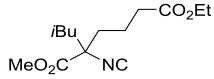
Yield: 68% yield (with isobutyl bromide)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.79 (s, 3H), 1.95 – 1.77 (m, 4H), 1.80 – 1.60 (m, 2H), 1.00 (d, *J* = 6.3 Hz, 6H), 0.84 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.4, 159.9 (br. s), 66.9 (t *J* = 6.0 Hz), 53.2, 49.0, 25.0, 23.9, 22.4.

IR: 2959 (m), 2365 (w), 2343 (w), 2137 (m), 1748 (s), 1473 (w), 1440 (w), 1235 (s), 1150 (s).

HRMS: (ESI) calcd for $C_{12}H_{21}NNaO_2^+$ $[M+Na]^+$ 234.1464; found 234.1469.



General procedure C

Aspect: yellow oil

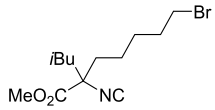
Yield: 71% yield (with ethyl 4-iodobutanoate)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 4.13 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 2.38 – 2.28 (m, 2H), 2.01 – 1.82 (m, 4H), 1.80 – 1.72 (m, 2H), 1.63 – 1.48 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 172.7, 169.8, 159.9, 67.5, 60.7, 53.5, 47.2, 40.0, 33.5, 25.1, 23.8, 22.2, 19.6, 14.4.

IR: 2960 (w), 2137 (w), 1733 (s), 1450 (w), 1235 (m), 1172 (s), 1136 (m), 1028 (w).

HRMS: (ESI) calcd for $C_{14}H_{23}NNaO_4^+$ $[M+Na]^+$ 292.1519; found 292.1524.



General procedure C

Aspect: yellow oil

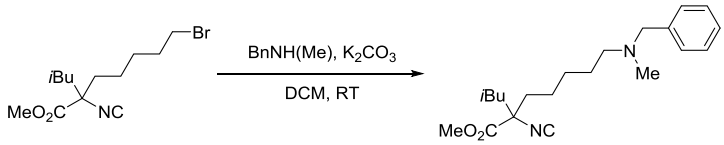
Yield: 60% yield (with 1,5-dibromopentane)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.40 (t, *J* = 6.7 Hz, 2H), 1.96 – 1.81 (m, 5H), 1.80 – 1.70 (m, 2H), 1.67 – 1.54 (m, 1H), 1.45 (p, *J* = 7.5 Hz, 2H), 1.28 – 1.15 (m, 1H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 169.9, 159.5, 67.6, 53.3, 47.3, 40.6, 33.6, 32.3, 27.6, 25.0, 23.7, 23.2, 22.1.

IR: 2959 (m), 2873 (w), 2137 (m), 1749 (s), 1440 (w), 1235 (s), 1162 (m), 1009 (w).

HRMS: (ESI) calcd for $C_{13}H_{22}BrNNaO_2^+$ $[M+Na]^+$ 326.0726; found 326.0723.



To a solution of alkyl bromide **X** in DCM were added K2CO3 (5 eqiv.) and N,N-(benzyl)methyl (2 equiv.). The reaction mixture was stirred at RT for 24 hours. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with DCM (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

Yield: 54% yield

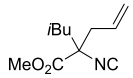
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.34 – 7.29 (m, 4H), 7.25 – 7.21 (m, 1H), 3.79 (s, 3H), 3.48 (s, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.18 (s, 3H), 1.94 – 1.80 (m, 3H), 1.79 – 1.66 (m, 2H), 1.64 – 1.57 (m, 1H), 1.56 – 1.48 (m, 2H), 1.37 – 1.27 (m, 2H), 1.24 – 1.14 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.1, 159.5, 139.2, 129.2, 128.4, 127.1, 67.8, 62.4, 57.3, 53.3, 47.4, 42.3, 40.9, 27.1, 27.0, 25.1, 24.0, 23.8, 22.2.

IR: 3247 (w), 2955 (m), 2934 (m), 2865 (w), 2787 (w), 2361 (w), 2341 (w), 2137 (s), 1746 (s), 1455 (m), 1370 (w), 1235 (s), 1148 (m), 1019 (w), 741 (m), 700 (m).

HRMS: (ESI) calcd for $C_{34}H_{44}N_3O^+$ $[M+H]^+$ 510.3479; found 510.3481.



General procedure C

Aspect: yellow oil

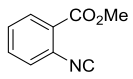
Yield: 78% yield (with allyl bromide)

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 5.78 (ddt, *J* = 17.3, 10.3, 7.3 Hz, 1H), 5.37 – 5.05 (m, 2H), 3.79 (s, 3H), 2.62 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.50 (dd, *J* = 13.9, 7.3 Hz, 1H), 1.95 – 1.81 (m, 2H), 1.81 – 1.72 (m, 1H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 169.6, 159.9, 130.1, 121.2, 67.6 (t, *J* = 6.0 Hz), 53.4, 46.6, 45.0, 25.1, 23.8, 22.1.

IR: 2959 (w), 2136 (m), 1747 (s), 1440 (w), 1222 (s), 1157 (m), 995 (w), 928 (m).

HRMS: (ESI) calcd for $C_{11}H_{18}NO_2^+$ $[M+H]^+$ 196.1332; found 196.1334.



From literature report [220]

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.07 – 7.91 (m, 1H), 7.57 (m, 1H), 7.47 (m, 2H), 3.97 (s, 3H).

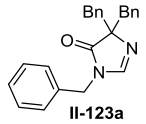
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 169.6, 164.6, 133.2, 131.5, 129.3, 129.0, 127.2, 125.7, 52.8.

IR: 2125 (w), 1722 (m), 1693 (m), 1585 (w), 1516 (w), 1449 (w), 1435 (m), 1297 (m), 1254 (s), 1134 (m), 1081 (s), 962 (w), 753 (s), 700 (w).

HRMS: (ESI) calcd for $C_9H_8NO_2^+$ $[M+H]^+$ 162.0550; found 162.0551.

- Silver-catalyzed isocyanide insertion/lactamization

3,5,5-trisubstituted-3,5-dihydro-4H-imidazol-4-one



II-123a

General procedure A

Yield: 32 mg, 90% yield, Eluent AcOEt/PE: 10:90 to 30:70

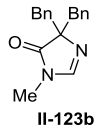
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.25 – 7.17 (m, 10H), 7.16 – 7.11 (m, 1H), 7.10 – 7.04 (m, 2H), 7.04 (s, 1H), 6.35 – 6.24 (m, 2H), 4.12 (s, 2H), 3.27 (d, *J* = 13.1 Hz, 2H), 3.21 (d, *J* = 13.1 Hz, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.2, 151.8, 135.0, 134.7, 130.3, 128.7, 127.9, 127.5, 126.8, 126.8, 77.1, 43.6, 43.0.

IR: 3062 (w), 2919 (w), 1706 (s), 1618 (m), 1455 (w), 1357 (w), 1141 (m), 942 (w), 739 (m), 697 (s).

HRMS: (ESI) calcd for $C_{24}H_{23}N_2O^+$ $[M+H]^+$ 355.1805; found 355.1803.



II-123b

General procedure A

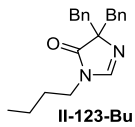
Yield: 27 mg, 98% yield, Eluent AcOEt/PE: 10:90 to 30:70

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.23 – 7.12 (m, 10H), 7.07 (s, 1H), 3.18 (d, *J* = 13.1 Hz, 2H), 3.11 (d, *J* = 13.1 Hz, 2H), 2.53 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 183.2, 152.5, 135.1, 130.1, 127.7, 126.7, 76.9, 42.7, 26.7.

IR: 3030 (w), 1716 (m), 1611 (m), 1495 (w), 1293 (m), 1089 (w), 742 (m), 700 (s).

HRMS: (ESI) calcd for $C_{18}H_{19}N_2O^+$ $[M+H]^+$ 279.1492; found 279.1499.



II-123-Bu

General procedure A

Yield: 31 mg, 97% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.22 – 7.12 (m, 10H), 7.09 (s, 1H), 3.19 (d, *J* = 13.1 Hz, 2H), 3.13 (d, *J* = 13.1 Hz, 2H), 2.92 (t, *J* = 7.0 Hz, 2H), 1.02 – 0.84 (m, 2H), 0.72 – 0.59 (m, 5H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.6, 152.3, 135.1, 130.2, 127.7, 126.7, 77.0, 42.8, 40.2, 30.3, 19.2, 13.4.

IR: 2922 (w), 1715 (m), 1612 (m), 1495 (w), 1351 (w), 1284 (w), 934 (w), 741 (m), 701 (s).

HRMS: (ESI) calcd for $C_{21}H_{25}N_2O^+$ $[M+H]^+$ 321.1961; found 321.1963.

II-123c

General procedure A

Yield: 29.2 mg, 96% yield, Eluent AcOEt/PE: 10:90 to 30:70

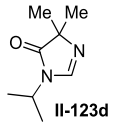
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.23 – 7.14 (m, 10H), 7.12 (s, 1H), 5.06 (ddt, *J* = 17.1, 10.5, 5.3 Hz, 1H), 4.79 (ddt, *J* = 10.3, 2.4, 0.8 Hz, 1H), 4.30 (ddt, *J* = 17.1, 1.7, 0.8 Hz, 1H), 3.56 (dt, *J* = 5.4, 1.6 Hz, 2H), 3.22 (d, *J* = 13.1 Hz, 2H), 3.16 (d, *J* = 13.1 Hz, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.2, 151.9, 135.1, 131.0, 130.3, 127.8, 126.8, 117.5, 77.2, 42.8, 42.2.

IR: 3030 (w), 2921 (w), 1721 (s), 1611 (m), 1495 (w), 1351 (w), 935 (w), 742 (m), 702 (s).

HRMS: (ESI) calcd for $C_{20}H_{21}N_2O^+$ $[M+H]^+$ 305.1648; found 305.1655.



II-123d

General procedure A

Yield: 14.6 mg, 95% yield, Eluent AcOEt/PE: 10:90 to 30:70

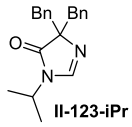
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.72 (s, 1H), 4.15 (sept, *J* = 6.9 Hz, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 1.31 (s, 6H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 184.9, 149.5, 68.9, 43.3, 23.6, 21.7.

IR: 2978 (w), 2929 (w), 1707 (s), 1605 (s), 1373 (w), 1295 (w), 1245 (w), 1221 (w).

HRMS: (ESI) calcd for $C_8H_{15}N_2O^+$ $[M+H]^+$ 155.1179; found 155.1179.



II-123-iPr

General procedure A

Yield: 29.1 mg, 95% yield, Eluent AcOEt/PE: 10:90 to 30:70

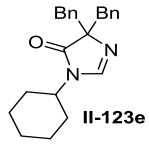
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.22 – 7.10 (m, 11H), 3.66 (sept, *J* = 6.9 Hz, 1H, 1H), 3.20 (d, *J* = 13.0 Hz, 2H), 3.13 (d, *J* = 13.0 Hz, 2H), 0.66 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.0, 150.0, 135.1, 130.2, 127.6, 126.6, 77.5, 42.6, 20.8.

IR: 3058 (w), 2972 (w), 1728 (w), 1707 (s), 1609 (m), 1375 (w), 1251 (m), 1076 (w), 880 (w), 743 (m), 699 (s).

HRMS: (ESI) calcd for $C_{20}H_{23}N_2O^+$ $[M+H]^+$ 307.1805; found 307.1799.



II-123e

General procedure A

Yield: 30.5 mg, 88% yield, Eluent AcOEt/PE: 10:90 to 30:70

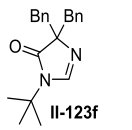
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.21 – 7.11 (m, 11H), 3.27 (tt, *J* = 12.5, 3.9 Hz, 1H), 3.21 (d, *J* = 13.0 Hz, 2H), 3.13 (d, *J* = 13.0 Hz, 2H), 1.65 – 1.49 (m, 3H), 1.19 – 1.06 (m, 2H), 1.06 – 0.97 (m, 2H), 0.98 – 0.88 (m, 1H), 0.87 – 0.74 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.2, 150.3, 135.2, 130.2, 127.7, 126.6, 50.1, 77.5, 42.7, 31.3, 25.2, 25.0.

IR: 3031 (w), 2933 (m), 2856 (w), 1725 (s), 1607 (s), 1496 (w), 1454 (w), 1264 (w), 1124 (m), 894 (w), 738 (m), 701 (s).

HRMS: (ESI) calcd for $C_{23}H_{27}N_2O^+$ $[M+H]^+$ 347.2118; found 347.2114.



II-123f

General procedure A

Yield: 21.8 mg, 68% yield, Eluent AcOEt/PE: 10:90 to 30:70

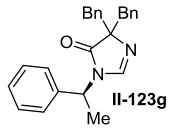
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.24 (s, 1H), 7.22 – 7.11 (m, 10H), 3.19 (d, *J* = 13.0 Hz, 2H), 3.11 (d, *J* = 13.2 Hz, 2H), 0.96 (s, 9H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 183.2, 151.0, 135.2, 130.4, 127.6, 126.6, 77.5, 54.2, 43.0, 27.4.

IR: 2922 (w), 1709 (s), 1602 (w), 1456 (w), 1281 (m), 1240 (m), 1170 (m), 1145 (w), 870 (w), 791 (w), 741 (m), 696 (s).

HRMS: (ESI) calcd for $C_{21}H_{25}N_2O^+$ $[M+H]^+$ 321.1961; found 321.1969.



II-123g

General procedure A

Yield: 33.2 mg, 90% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: white amorphous solid

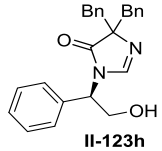
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.25 – 7.16 (m, 10H), 7.16 – 7.11 (m, 1H), 7.10 – 7.04 (m, 2H), 6.96 (s, 1H), 6.38 – 6.32 (m, 2H), 4.76 (q, *J* = 7.1 Hz, 1H), 3.30 (d, *J* = 13.1 Hz, 4H), 3.28 (d, J = 13.1 Hz, 4H), 3.25 (d, *J* = 13.1 Hz, 4H), 3.23 (d, *J* = 13.1 Hz, 1H), 0.89 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 181.5, 150.6, 138.8, 135.1, 134.9, 130.4, 130.4, 128.5, 128.0, 127.7, 127.4, 126.8, 126.8, 126.0, 77.6, 48.4, 43.2, 42.5, 18.2.

IR: 3061 (w), 2917 (w), 1710 (m), 1609 (m), 1455 (w), 1366 (w), 1160 (w), 743 (m), 699 (s).

HRMS: (ESI) calcd for $C_{25}H_{25}N_2O^+$ $[M+H]^+$ 369.1961; found 369.1951.

$[\alpha]_D^{25}$= - 43.8 (*c* 0.94, $CHCl_3$)



II-123h

General procedure A

Yield: 30.0 mg, 78% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: white amorphous solid

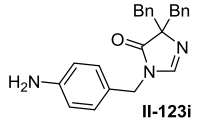
^{1}H NMR (400.13 MHz, MeOD): 7.58 (s, 1H), 7.25 – 7.18 (m, 3H), 7.17 – 7.05 (m, 10H), 6.56 – 6.40 (m, 2H), 4.63 (t, *J* = 5.4 Hz, 1H), 3.52 (dd, *J* = 11.6, 5.4 Hz, 1H), 3.30 – 3.25 (m, 1H), 3.24 (dd, *J* = 10.7, 2.5 Hz, 2H), 3.17 (dd, *J* = 13.2, 3.1 Hz, 2H).

^{13}C NMR (100.62 MHz, MeOD): 183.7, 154.5, 137.3, 136.1, 136.0, 131.3, 129.6, 129.1, 129.0, 128.5, 128.2, 128.1, 127.8, 78.0, 62.9, 57.1, 44.3, 43.5, 30.8.

IR: 2923 (w), 2363 (w), 1729 (m), 1609 (m), 1496 (w), 1456 (w), 1362 (w), 743 (w), 700 (s).

HRMS: (ESI) calcd for $C_{25}H_{25}N_2O_2^+$ $[M+H]^+$ 385.1911; found 385.1910.

$[\alpha]_D^{25}$= - 10.6 (*c* 0.43, $CHCl_3$)



II-123i

General procedure A

Yield: 34.7 mg, 94% yield, Eluent AcOEt/PE: 10:90 to 30:70

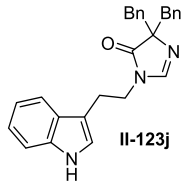
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.25 – 7.15 (m, 10H), 7.01 (s, 1H), 6.38 (d, *J* = 8.4 Hz, 2H), 6.13 (d, *J* = 8.4 Hz, 2H), 3.99 (s, 2H), 3.25 (d, *J* = 13.1 Hz, 2H), 3.19 (d, *J* = 13.1 Hz, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.1, 152.0, 145.8, 135.1, 130.3, 128.3, 127.9, 126.7, 124.3, 115.1, 77.2, 43.3, 42.9.

IR: 3424 (w), 3344 (w), 1699 (s), 1609 (s), 1519 (m), 1365 (m), 1272 (m), 1177 (m), 1147 (m), 829 (m), 734 (s).

HRMS: (ESI) calcd for $C_{24}H_{24}N_3O^+$ $[M+H]^+$ 370.1914; found 370.1905.



II-123j

General procedure A

Yield: 39.9 mg, 98% yield, Eluent AcOEt/PE: 10:90 to 30:70

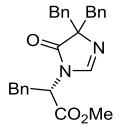
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.91 – 7.88 (br. s, 1H), 7.44 – 7.36 (m, 1H), 7.32 – 7.28 (m, 1H), 7.25 – 7.17 (m, 10H), 7.17 – 7.14 (m, 1H), 7.10 – 7.05 (m, 1H), 6.58 (s, 1H), 5.94 (d, *J* = 2.3 Hz, 1H), 3.28 (t, *J* = 6.7 Hz, 2H), 3.23 (d, *J* = 13.1 Hz, 2H), 3.15 (d, *J* = 13.1 Hz, 2H), 2.42 (t, *J* = 6.7 Hz, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.6, 152.6, 136.2, 135.3, 130.5, 127.8, 126.8, 126.3, 122.7, 122.2, 119.5, 118.3, 111.4, 111.3, 76.6, 42.9, 40.5, 24.7.

IR: 3031 (w), 2920 (w), 1716 (m), 1607 (m), 1456 (w), 1355 (w), 1088 (w), 908 (m), 730 (s), 700 (s).

HRMS: (ESI) calcd for $C_{27}H_{26}N_3O^+$ $[M+H]^+$ 408.2070; found 408.2076.



II-123l

General procedure A

Yield: 29.9 mg, 70% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: white amorphous solid

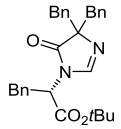
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.32 – 7.26 (m, 2H), 7.25 – 7.18 (m, 3H), 7.18 – 7.07 (m, 8H), 6.69 (s, 1H), 6.44 – 6.34 (m, 2H), 4.69 (dd, *J* = 6.8, 4.7 Hz, 1H), 3.44 (s, 3H), 3.17 (d, *J* = 13.1 Hz, 1H), 3.13 (s, 2H), 3.11 (d, *J* = 13.1 Hz, 1H), 3.08 (d, *J* = 13.1 Hz, 1H), 2.78 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.44 (dd, *J* = 13.8, 6.8 Hz, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 181.9, 169.0, 150.7, 135.3, 134.8, 134.6, 130.7, 130.3, 129.4, 128.7, 128.0, 127.7, 127.4, 127.1, 126.7, 76.0, 53.5, 52.5, 43.0, 42.5, 37.6.

IR: 3030 (w), 2922 (w), 1730 (s), 1609 (m), 1496 (w), 1456 (w), 1226 (w), 741 (w), 701 (s).

HRMS: (ESI) calcd for $C_{27}H_{27}N_2O_3^+$ $[M+H]^+$ 427.2016; found 427.2017.

$[\alpha]_D^{25}$= + 20.3 (*c* 0.96, $CHCl_3$)



II-123m

General procedure A

Yield: 34.7 mg, 74% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: white amorphous solid

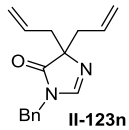
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 7.18 – 7.07 (m, 8H), 6.86 (s, 1H), 6.45 – 6.43 (m, 2H), 4.57 (dd, *J* = 7.3, 4.6 Hz, 1H), 3.17 (d, *J* = 13.1 Hz, 1H), 3.14 (s, 2H), 3.11 (d, *J* = 13.1 Hz, 1H), 2.65 (dd, *J* = 13.8, 4.6 Hz, 1H), 2.37 (dd, *J* = 13.7, 7.4 Hz, 1H), 1.21 (s, 9H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.0, 167.5, 151.1, 135.3, 134.9, 134.7, 130.7, 130.2, 129.6, 128.4, 127.9, 127.8, 127.3, 127.1, 126.8, 82.9, 75.9, 54.0, 42.9, 42.6, 38.0, 27.7.

IR: 2899 (w), 1737 (m), 1720 (s), 1614 (m), 1370 (w), 1233 (w), 1146 (s), 741 (w), 700 (m).

HRMS: (ESI) calcd for $C_{30}H_{33}N_2O_3^+$ $[M+H]^+$ 469.2486; found 469.2487.

$[\alpha]_D^{25}$= + 36.5 (*c* 0.85, $CHCl_3$)



II-123n

General procedure A

Yield: 20.6 mg, 81% yield, Eluent AcOEt/PE: 10:90 to 30:70

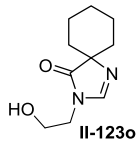
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.39 – 7.28 (m, 3H), 7.25 – 7.17 (m, 2H), 5.70 – 5.42 (m, 2H), 5.10 (dd, *J* = 17.1, 1.7 Hz, 2H), 5.02 (dd, *J* = 10.2, 2.0 Hz, 2H), 4.58 (s, 2H), 2.57 (d, J = 13.6 Hz, 1H), 2.55 (d, *J* = 13.6 Hz, 1H), 2.49 (d, *J* = 13.6 Hz, 1H), 2.47 (d, *J* = 13.6 Hz, 1H)

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.9, 152.1, 135.5, 131.4, 128.9, 128.2, 127.9, 119.4, 74.9, 44.5, 40.4.

IR: 2934 (w), 1727 (s), 1608 (s), 1437 (w), 1350 (m), 1166 (m), 923 (m), 720 (m), 700 (m).

HRMS: (ESI) calcd for $C_{16}H_{19}N_2O^+$ $[M+H]^+$ 255.1492; found 255.1499.



II-123o

General procedure A

Yield: 15.5 mg, 79% yield, Eluent AcOEt/PE: 10:90 to 30:70

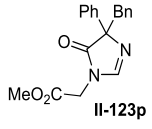
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.85 (s, 1H), 3.90 – 3.68 (m, 2H), 3.68 – 3.55 (m, 2H), 2.78 (s, 1H), 1.86 – 1.60 (m, 7H), 1.55 – 1.33 (m, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 185.9, 152.8, 71.1, 60.9, 43.5, 33.0, 25.1, 21.5.

IR: 2934 (m), 2855 (w), 1720 (s), 1609 (s), 1448 (w), 1362 (m), 1291 (w), 1181 (w), 1054 (m), 1012 (w).

HRMS: (ESI) calcd for $C_{10}H_{17}N_2O_2^+$ $[M+H]^+$ 197.1285; found 197.1285.



II-123p

General procedure A

Yield: 30.6 mg, 95% yield, Eluent AcOEt/PE: 10:90 to 30:70

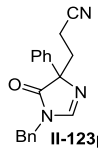
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.76 – 7.67 (m, 2H), 7.62 (s, 1H), 7.42 – 7.34 (m, 2H), 7.33 – 7.27 (m, 1H), 7.23 – 7.17 (m, 3H), 7.16 – 7.09 (m, 2H), 4.06 (d, *J* = 17.9 Hz, 1H), 3.92 (d, *J* = 17.9 Hz, 1H), 3.64 (s, 3H), 3.43 (d, *J* = 13.2 Hz, 1H), 3.37 (d, *J* = 13.2 Hz, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 181.5, 167.6, 151.7, 138.3, 134.8, 130.6, 128.6, 128.0, 127.9, 127.0, 126.2, 76.6, 52.9, 46.3, 41.5.

IR: 3031 (w), 1730 (s), 1617 (m), 1496 (w), 1438 (w), 1377 (w), 1334 (w), 1277 (m), 1218 (s), 1163 (m), 955 (m), 767 (w), 700 (s).

HRMS: (ESI) calcd for $C_{19}H_{19}N_2O_3^+$ $[M+H]^+$ 323.1390; found 323.1390.



II-123p

General procedure A

Yield: 20.9 mg, 69% yield, Eluent AcOEt/PE: 10:90 to 30:70

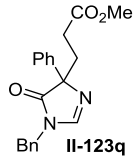
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.70 – 7.53 (m, 2H), 7.48 – 7.29 (m, 6H), 7.23 – 7.16 (m, 2H), 4.68 (d, *J* = 15.1 Hz, 1H), 4.58 (d, *J* = 15.2 Hz, 1H), 2.57 – 2.46 (m, 1H), 2.43 – 2.29 (m, 1H), 2.29 – 2.17 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 181.5, 153.6, 136.5, 135.1, 129.4, 129.0, 128.7, 128.6, 127.9, 126.1, 119.0, 74.3, 45.1, 35.3, 12.6.

IR: 3064 (w), 1727 (s), 1611 (s), 1448 (m), 1346 (m), 1265 (m), 1167 (m), 720 (m), 699 (s).

HRMS: (ESI) calcd for $C_{19}H_{17}N_3NaO^+$ $[M+Na]^+$ 326.1264; found 326.1268.



II-123q

General procedure A

Yield: 27.6 mg, 82% yield, Eluent AcOEt/PE: 10:90 to 30:70

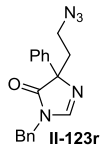
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.68 – 7.59 (m, 2H), 7.39 – 7.27 (m, 6H), 7.23 – 7.16 (m, 2H), 4.66 (d, *J* = 15.2 Hz, 1H), 4.55 (d, *J* = 15.2 Hz, 1H), 3.60 (s, 3H), 2.58 – 2.43 (m, 1H), 2.39 – 2.16 (m, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.0, 173.0, 152.7, 137.5, 135.2, 129.1, 128.5, 128.3, 127.9, 127.7, 126.0, 74.9, 51.6, 44.7, 34.7, 28.9.

IR: 2947 (w), 1726 (s), 1612 (m), 1437 (m), 1347 (m), 1265 (m), 1165 (m), 762 (w), 727 (m), 699 (s).

HRMS: (ESI) calcd for $C_{20}H_{21}N_2O_3^+$ $[M+H]^+$ 337.1547; found 337.1547.



II-123r

General procedure A

Yield: 31.0 mg, 97% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: white amorphous solid

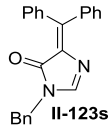
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.70 – 7.56 (m, 2H), 7.43 – 7.29 (m, 6H), 7.25 – 7.20 (m, 2H), 4.69 (d, *J* = 15.1 Hz, 1H), 4.56 (d, *J* = 15.1 Hz, 1H), 3.26 – 3.21 (m, 2H), 2.50 – 2.36 (m, 1H), 2.36 – 2.25 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 181.8, 153.1, 137.8, 135.1, 129.2, 128.7, 128.4, 128.1, 127.8, 125.8, 73.9, 47.0, 45.0, 38.6.

IR: 2931 (w), 2096 (s), 1726 (s), 1611 (s), 1448 (w), 1346 (m), 1266 (m), 1167 (m), 762 (w), 699 (s).

HRMS: (ESI) calcd for $C_{18}H_{17}N_5NaO^+$ $[M+Na]^+$ 342.1325; found 342.1326.

$[\alpha]_D^{25}$= - 11.7 (*c* 2.73, $CHCl_3$)



II-123s

General procedure A

Yield: 27.1 mg, 80% yield, Eluent AcOEt/PE: 10:90 to 30:70

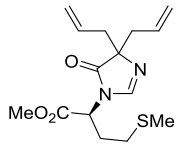
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.54 – 7.48 (m, 2H), 7.47 – 7.40 (m, 3H), 7.39 – 7.31 (m, 8H), 7.31 – 7.27 (m, 2H), 4.69 (s, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 167.6, 151.3, 150.1, 139.1, 137.2, 135.9, 135.7, 132.3, 130.6, 129.7, 129.5, 129.0, 128.2, 128.0, 127.9, 127.8, 44.9.

IR: 3057 (w), 1701 (s), 1597 (m), 1444 (w), 1267 (m), 1166 (m), 761 (m), 721 (m), 696 (s).

HRMS: (ESI) calcd for $C_{23}H_{19}N_2O^+$ $[M+H]^+$ 339.1492; found 339.1495.



II-123t

General procedure A

Yield: 24.8 mg, 80% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: white amorphous solid

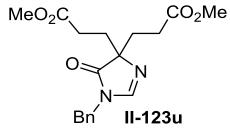
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.79 (s, 1H), 5.66 – 5.37 (m, 2 H), 5.11 (dq, *J* = 17.1, 1.6 Hz, 2H), 5.05 (br. d, *J* = 10.2 Hz, 2H), 5.01 – 4.96 (m, 2H), 4.71 (dd, *J* = 10.3, 4.4 Hz, 1H), 3.70 (s, 3H), 2.58 – 2.47 (m, 2H), 2.47 – 2.37 (m, 3H), 2.36 – 2.19 (m, 2H), 2.09 – 2.03 (m, 1H), 2.02 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.3, 170.0, 150.8, 131.4, 131.2, 119.7, 119.4, 74.9, 52.9, 52.2, 40.7, 40.2, 30.0, 29.9, 15.3.

IR: 2917 (w), 1733 (s), 1610 (m), 1436 (w), 1377 (w), 1242 (m), 1201 (w), 998 (w), 924 (w).

HRMS: (ESI) calcd for $C_{15}H_{23}N_2O_3S^+$ $[M+H]^+$ 311.1424; found 311.1424.

$[\alpha]_D^{25}$= - 9.7 (*c* 0.96, $CHCl_3$)



II-123u

General procedure A

Yield: 31.9 mg, 92% yield, Eluent AcOEt/PE: 10:90 to 30:70

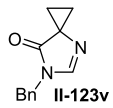
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.48 – 7.32 (m, 3H), 7.31 – 7.20 (m, 2H), 4.61 (s, 2H), 3.64 (s, 6H), 2.33 – 2.03 (m, 8H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.8, 172.8, 153.0, 135.2, 129.2, 128.5, 127.9, 73.0, 51.7, 44.8, 31.1, 28.3.

IR: 2952 (w), 1727 (s), 1607 (m), 1437 (m), 1350 (w), 1264 (m), 1199 (m), 1168 (m), 705 (m).

HRMS: (ESI) calcd for $C_{18}H_{23}N_2O_5^+$ $[M+H]^+$ 347.1601; found 347.1613.



II-123v

General procedure A

Yield: 14.8 mg, 74% yield, Eluent AcOEt/PE: 10:90 to 30:70

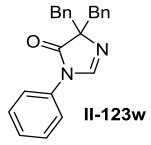
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.41 – 7.31 (m, 3H), 7.30 – 7.26 (m, 2H), 4.72 (s, 2H), 1.81 – 1.73 (m, 2H), 1.73 – 1.67 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 180.8, 151.9, 135.6, 129.1, 128.2, 51.9, 45.2, 19.4.

IR: 3032 (w), 1714 (s), 1585 (s), 1456 (w), 1378 (w), 1347 (m), 1294 (m), 1142 (m), 1046 (m), 956 (m), 737 (m), 716 (s), 697 (s).

HRMS: (ESI) calcd for $C_{12}H_{13}N_2O^+$ $[M+H]^+$ 201.1022; found 201.1028.



II-123w

General procedure A

Yield: 16.3 mg, 48% yield, Eluent AcOEt/PE: 10:90 to 30:70

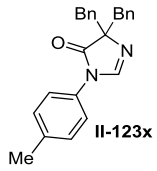
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.41 (s, 1H), 7.31 – 7.27 (m, 2H), 7.26 – 7.20 (m, 11H), 6.63 – 6.54 (m, 2H), 3.36 (d, *J* = 13.1 Hz, 2H), 3.30 (d, *J* = 13.2 Hz, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 180.7, 151.6, 134.8, 132.8, 130.3, 129.4, 128.7, 127.9, 127.0, 123.2, 77.5, 42.9.

IR: 2923 (w), 1723 (s), 1615 (w), 1597 (w), 1503 (m), 1456 (w), 1378 (w), 1191 (w), 911 (w), 760 (w), 741 (m), 702 (s), 689 (m).

HRMS: (ESI) calcd for $C_{23}H_{21}N_2O^+$ $[M+H]^+$ 341.1648; found 341.1651.



II-123x

General procedure A

Yield: 16.3 mg, 46% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.30 (s, 1H), 7.25 – 7.18 (m, 10H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.47 (d, *J* = 8.0 Hz, 2H) 3.33 (d, *J* = 13.1 Hz, 2H), 3.25 (d, *J* = 13.1 Hz, 2H), 2.28 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 180.9, 151.8, 138.0, 134.8, 130.3, 129.9, 127.9, 127.0, 125.2, 123.2, 75.0, 42.9, 21.0.

IR: 3031 (w), 1733 (m), 1608 (m), 1516 (m), 1377 (w), 1188 (m), 915 (w), 818 (w), 743 (m), 701 (s).

HRMS: (ESI) calcd for $C_{24}H_{23}N_2O^+$ $[M+H]^+$ 355.1805; found 355.1805.

II-123y

General procedure A

Yield: 19.7 mg, 51% yield, Eluent AcOEt/PE: 10:90 to 30:70

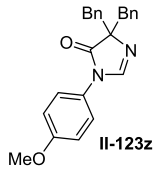
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.13 (d, *J* = 9.0 Hz, 2H), 7.46 (s, 1H), 7.24 – 7.14 (m, 10H), 6.94 (d, *J* = 9.0 Hz, 2H), 3.34 (d, *J* = 13.2 Hz, 2H), 3.27 (d, *J* = 13.2 Hz, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 180.6, 149.3, 146.1, 138.5, 134.7, 130.3, 128.1, 127.3, 125.1, 122.1, 78.5, 43.1.

IR: 2924 (w), 1737 (m), 1618 (w), 1594 (s), 1521 (s), 1498 (s), 1344 (s), 1177 (m), 851 (m), 741 (m), 702 (s).

HRMS: (ESI) calcd for $C_{23}H_{20}N_3O_3^+$ $[M+H]^+$ 386.1499; found 386.1502.



II-123z

General procedure A

Yield: 20.4 mg, 55% yield, Eluent AcOEt/PE: 10:90 to 30:70

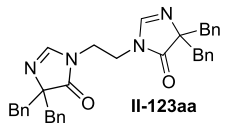
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.25 (s, 1H), 7.25 – 7.18 (m, 10H), 6.80 – 6.72 (m, 2H), 6.49 – 6.41 (m, 2H), 3.74 (s, 3H), 3.32 (d, *J* = 13.1 Hz, 2H), 3.24 (d, *J* = 13.1 Hz, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 181.2, 159.1, 151.9, 135.0, 130.3, 127.9, 126.9, 125.6, 125.2, 114.6, 70.6, 55.5, 42.9.

IR: 2923 (w), 1733 (s), 1614 (m), 1250 (s), 1185 (m), 1032 (w), 831 (w), 745 (w), 703 (s).

HRMS: (ESI) calcd for $C_{24}H_{23}N_2O_2^+$ $[M+H]^+$ 371.1754; found 371.1769.



II-123aa

General procedure A

Yield: 41.6 mg, 75% yield, Eluent AcOEt/PE: 10:90 to 30:70

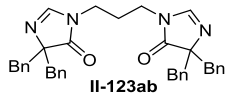
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.20 – 7.11 (m, 12H), 7.10 – 7.03 (m, 8H), 5.08 (s, 2H), 3.10 (d, *J* = 2.4 Hz, 8H), 2.46 (s, 4H)

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.5, 151.5, 135.0, 130.5, 128.0, 127.2, 76.7, 42.7, 39.6.

IR: 3030 (w), 2922 (w), 1730 (s), 1608 (s), 1455 (m), 1364 (m), 913 (m), 741 (m), 702 (s).

HRMS: (ESI) calcd for $C_{36}H_{35}N_4O_2^+$ $[M+H]^+$ 555.2755; found 555.2756.



II-123ab

General procedure A

Yield: 45.5 mg, 80% yield, Eluent AcOEt/PE: 10:90 to 30:70

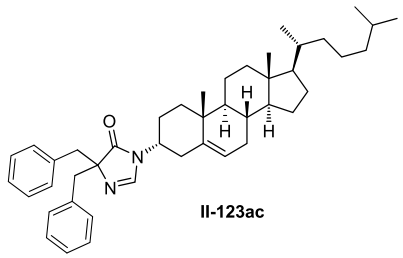
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.13 – 7.06 (m, 16H), 7.08 – 6.99 (m, 4H), 6.84 (s, 2H), 3.11 (s, 8H), 1.97 – 1.89 (m, 4H), 0.75 – 0.65 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.4, 152.2, 135.0, 130.2, 127.7, 126.8, 77.1, 42.7, 36.1, 26.5.

IR: 3030 (w), 2921 (w), 1722 (m), 1609 (m), 1354 (w), 1088 (w), 740 (m), 700 (s).

HRMS: (ESI) calcd for $C_{18}H_{23}N_2O_5^+$ $[M+H]^+$ 347.1601; found 347.1613.



II-123ac

General procedure A

Yield: 46.2 mg, 73% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: white amorphous solid

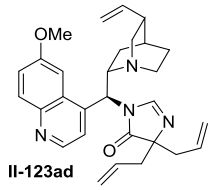
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.24 – 7.10 (m, 10H), 5.06 – 5.04 (m, 1H), 3.79 – 3.71 (m, 1H), 3.16 – 3.07 (m, 4H), 2.50 – 2.32 (m, 1H), 2.04 – 1.96 (m, 1H), 1.95 – 1.77 (m, 2H), 1.62 – 1.20 (m, 13H), 1.18 – 0.94 (m, 9H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.84 (s, 3H), 0.70 – 0.65 (m, 1H), 0.63 (s, 3H), 0.06 – -0.13 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 183.1, 152.0, 139.0, 135.4, 135.3, 130.5, 130.4, 127.8, 127.8, 126.9, 126.8, 123.9, 75.7, 56.8, 56.2, 49.9, 47.5, 43.0, 42.4, 42.4, 39.8, 39.7, 36.8, 36.3, 35.9, 35.0, 31.9, 31.8, 31.6, 28.3, 28.2, 25.2, 24.3, 23.9, 23.0, 22.7, 20.6, 19.3, 18.9, 12.0.

IR: 2934 (w), 2867 (w), 1725 (m), 1602 (w), 1456 (w), 1364 (w), 1283 (w), 738 (m), 700 (s).

HRMS: (ESI) calcd for $C_{44}H_{61}N_2O^+$ $[M+H]^+$ 633.4778; found 633.4778.

$[\alpha]_D^{25}$= - 24 (*c* 0.42, $CHCl_3$)



II-123ad

General procedure A

Yield: 32.9 mg, 70% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: white amorphous solid

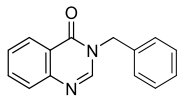
^{1}H NMR (400.13 MHz, MeOD): 8.69 – 8.60 (m, 1H), 8.03 (s, 1H), 7.97 – 7.90 (m, 1H), 7.75 (br. s, 1H), 7.61 – 7.52 (m, 1H), 7.47 – 7.40 (m, 1H), 6.04 – 5.89 (m, 1H), 5.74 – 5.60 (m, 2H), 5.57 – 5.43 (m, 1H), 5.22 – 5.14 (m, 1H), 5.14 – 5.09 (m, 1H), 5.06 – 4.97 (m, 2H), 4.92 – 4.83 (m, 2H), 4.02 (s, 3H), 3.30 – 3.21 (m, 1H), 3.11 – 3.00 (m, 2H), 2.99 – 2.89 (m, 2H), 2.86 – 2.72 (m, 2H), 2.69 – 2.53 (m, 2H), 2.38 – 2.28 (m, 1H), 1.70 – 1.53 (m, 3H), 1.26 – 1.17 (m, 1H), 1.16 – 1.05 (m, 1H).

^{13}C NMR (100.62 MHz, MeOD): 173.5, 163.0, 161.4, 159.6, 148.2, 144.9, 142.2, 133.4, 133.3, 131.1, 130.3, 123.8, 121.0, 119.5, 119.4, 115.0, 103.1, 63.9, 60.6, 56.3, 51.0, 50.1, 48.2, 40.5, 40.1, 39.6, 28.9, 27.7, 26.7.

IR: 2936 (w), 1652 (s), 1622 (m), 1509 (s), 1476 (s), 1229 (s), 1030 (w), 995 (w), 919 (m), 850 (w), 829 (w), 736 (w), 715 (w).

HRMS: (ESI) calcd for $C_{29}H_{35}N_4O_2^+$ $[M+H]^+$ 471.2755; found 471.2755.

$[\alpha]_D^{25}$= + 59.8 (*c* 1.13, $CHCl_3$)



II-151

General procedure A

Yield: 20.3 mg, 86% yield, Eluent AcOEt/PE: 10:90 to 30:70

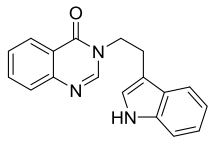
Aspect: white amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.33 (ddd, *J* = 8.0, 1.5, 0.6 Hz, 1H), 8.11 (s, 1H), 7.76 (ddd, *J* = 8.0, 6.9, 1.5 Hz, 1H), 7.71 (ddd, *J* = 8.0, 1.5, 0.6 Hz, 1H), 7.51 (ddd, *J* = 8.0, 6.9, 1.5 Hz, 1H), 7.38 – 7.33 (m, 4H), 7.33 – 7.28 (m, 1H), 5.20 (s, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 161.0, 148.0, 146.3, 135.7, 134.3, 129.0, 128.3, 128.0, 127.5, 127.4, 126.9, 122.2, 49.6.

IR: 3062 (w), 1733 (w), 1673 (s), 1474 (m), 1370 (m), 1323 (w), 775 (m), 750 (w), 711 (m), 696 (m).

HRMS: (ESI) calcd for $C_{15}H_{13}N_2O^+$ $[M+H]^+$ 237.1022; found 237.1027.



II-153

General procedure A

Yield: 23.7 mg, 82% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: white amorphous solid

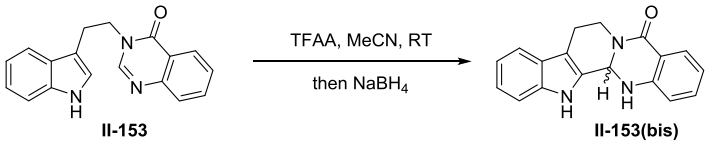
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.37 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.16 (br. s, 1H), 7.75 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.54 (s, 1H), 7.53 – 7.50 (m, 1H), 7.36 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.87 (d, *J* = 2.2 Hz, 1H), 4.30 (t, *J* = 6.7 Hz, 2H), 3.27 (t, *J* = 6.7 Hz, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 161.0, 147.8, 146.8, 136.5, 134.3, 127.2, 127.2, 126.8, 126.7, 122.8, 122.5, 122.0, 119.8, 118.4, 111.6, 111.3, 47.6, 24.9.

IR: 3312 (w), 1666 (s), 1610 (s), 1474 (m), 1376 (w), 1158 (w), 774 (m), 744 (m), 699 (w).

HRMS: (ESI) calcd for $C_{18}H_{16}N_3O^+$ $[M+H]^+$ 290.1288; found 290.1288.

Natural products synthesis:



II-153 **II-153(bis)**

Procedure: To a solution of compound **X** (57.9 mg, 0.2 mmol, 1 equiv) in MeCN (2 mL) was added TFAA (42 µL, 0.3 mmol, 1.5 equiv). The reaction mixture was stirred 1 hour at RT and $NaBH_4$ (0.4 nnol, 2 equiv) was added. The reaction mixture was stirred 1 hour at RT and quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with AcOEt (5 times). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product without further purification.

Yield: 80% overall yield

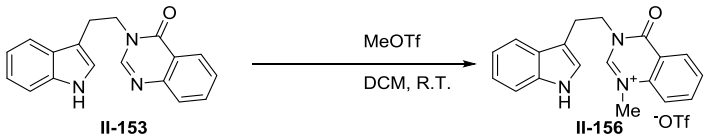
Aspect: yellow amorphous solid

^{1}H NMR (400.13 MHz, DMSO-d_6): δ 10.90 (s, 1H), 7.76 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.42 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.35 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1H), 7.14 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.04 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.90 (s, 1H), 6.89 – 6.77 (m, 2H), 6.05 (t, *J* = 1.5 Hz, 1H), 4.86 – 4.74 (m, 1H), 3.08 – 2.97 (m, 1H), 2.88 – 2.72 (m, 2H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ 163.8, 147.3, 136.4, 133.4, 130.8, 128.2, 125.9, 122.0, 119.1, 118.7, 118.6, 116.1, 115.3, 111.7, 109.5, 63.8, 38.8, 20.1.

IR: 3305 (w), 2925 (w), 2360 (w), 1731 (w), 1615 (s), 1489 (m), 1419 (m), 1308 (m), 1169 (m), 738 (s), 695 (m).

HRMS: (ESI) calcd for $C_{18}H_{16}N_3O^+$ $[M+H]^+$ 290.1288; found 290.1298.



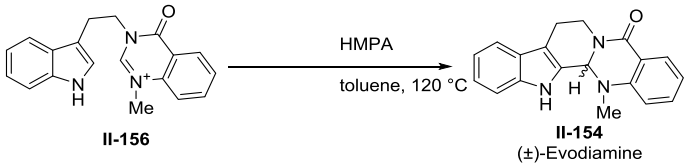
Aspect: yellow amorphous solid

^{1}H NMR (400.13 MHz, MeOD) δ 9.00 (s, 1H), 8.50 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.12 (t, *J* = 7.6 Hz, 1H), 7.90 (t, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 4.43 (t, *J* = 7.0 Hz, 2H), 3.75 (s, 3H), 3.33 – 3.28 (m, 2H).

^{13}C NMR (100.62 MHz, MeOD): δ 159.0, 154.0, 139.3, 138.2, 138.0, 131.4, 129.6, 128.5, 125.0, 122.9, 121.4, 120.2, 119.1, 118.5, 112.7, 110.6, 51.9, 49.6, 40.6, 24.9.

IR: 3320 (w), 1713 (s), 1662 (m), 1276 (s), 1260 (s), 1171 (m), 1031 (s), 756 (s).

HRMS: (ESI) calcd for $C_{19}H_{18}N_3O$ [M+] 304.1444; found 304.1449..



Yield: 18.8 mg, 62% yield Eluent DCM/MeOH: 100:0 to 95:5

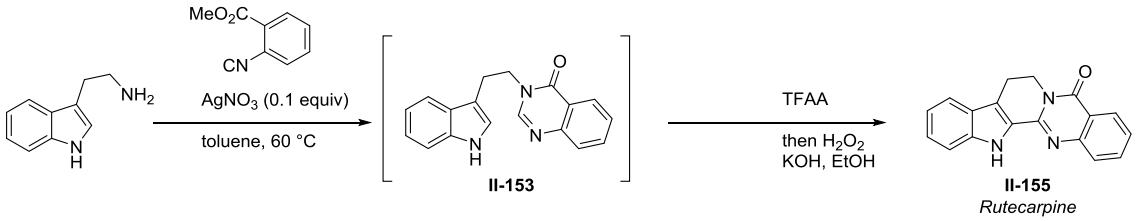
Aspect: yellow amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.23 – 7.17 (m, 2H), 7.14 (d, *J* = 8.1 Hz, 1H), 5.92 (s, 1H), 5.03 – 4.66 (m, 1H), 3.44 – 3.21 (m, 1H), 3.05 – 2.81 (m, 2H), 2.50 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 164.9, 150.8, 136.8, 133.2, 129.1, 128.4, 126.4, 124.3, 123.9, 123.2, 122.6, 120.2, 119.1, 113.8, 111.5, 69.0, 39.7, 37.4, 20.3.

IR: 3248 (w), 2922 (w), 1732 (w), 1638 (s), 1606 (m), 1481 (m), 1424 (s), 1168 (m), 910 (m), 744 (s), 617 (m).

HRMS: (ESI) calcd for $C_{19}H_{18}N_3O^+$ $[M+H]^+$ 304.1444; found 304.1438.



Procedure: To a solution of tryptamine (32.0 mg, 0.2 mmol, 1 equiv) and methyl *o*-isocyanobenzoate (35.5 mg, 0.22 mmol, 1.1 equiv) in MeCN (2 mL) was added $AgNO_3$ (3.4 mg, 0.02 mmol, 0.1 equiv)**.** The reaction mixture was stirred at 60 °C until complete consumption of the starting material (TLC monitoring, 12 hours). The reaction mixture was cooled to RT and TFAA (42 µL, 0.3 mmol, 1.5 equiv) was added. The reaction mixture was stirred 1 hour at RT and EtOH (2 mL) and a 3M aqueous solution of KOH (0.2 mL) was added. The reaction mixture was stirred 1 hour at 60 °C. The reaction was cooled to RT and H_2O_2 (1 mL) was added. The reaction mixture was stirred 12 hour at 60 °C. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with AcOEt (3 times). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (7:3 to 1:1 PE/AcOEt) to afford the pure product.

Yield: 43% overall yield

Aspect: yellow amorphous solid

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 9.44 (s, 1H), 8.39 – 8.21 (m, 1H), 7.77 – 7.66 (m, 2H), 7.65 – 7.62 (m, 1H), 7.47 – 7.38 (m, 2H), 7.36 – 7.30 (m, 1H), 7.23 – 7.14 (m, 1H), 4.59 (t, *J* = 6.9 Hz, 2H), 3.24 (t, *J* = 6.9 Hz, 2H).

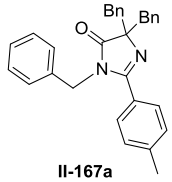
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 161.4, 147.1, 145.0, 138.5, 134.5, 127.3, 126.7, 126.4, 126.2, 125.8, 125.5, 121.0, 120.7, 120.1, 118.8, 112.2, 41.2, 19.7.

IR: 2958 (w), 2359 (m), 2343 (w), 1732 (s), 1677 (m), 1596 (s), 1471 (m), 1330 (w), 1234 (w), 1167 (m), 1149 (w), 771 (w), 749 (w), 738 (w).

HRMS: (ESI) calcd for $C_{18}H_{14}N_3O^+$ $[M+H]^+$ 288.1131; found 288.1132.

- Pd/Cu-catalyzed 3-CR reaction

2,3,5,5-tetrasubstituted-3,5-dihydro-4H-imidazol-4-one



II-167a

General procedure B

Yield: 32.0 mg, 72% yield, Eluent AcOEt/PE: 10:90 to 30:70

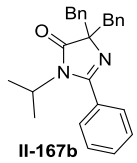
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.31 – 7.19 (m, 10H), 7.10 – 7.03 (m, 1H), 7.01 – 6.94 (m, 4H), 6.68 (d, *J* = 7.6 Hz, 2H), 6.09 (d, *J* = 7.6 Hz, 2H), 4.04 (s, 2H), 3.37 (s, 4H), 2.28 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 183.7, 162.3, 140.8, 135.9, 135.5, 130.8, 130.5, 129.1, 128.4, 128.0, 127.6, 127.0, 126.9, 126.1, 76.6, 44.3, 43.5, 21.5.

IR: 3030 (w), 2919 (w), 1729 (s), 1625 (w), 1495 (w), 1455 (m), 1379 (w), 1356 (m), 1125 (m), 968 (w), 821 (w), 750 (w), 724 (m), 701 (s).

HRMS: (ESI) calcd for $C_{31}H_{29}N_2O^+$ $[M+H]^+$ 445.2274; found 445.2284.



II-167b

General procedure B

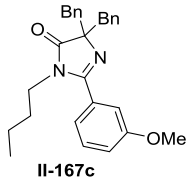
Yield: 19.5 mg, 51% yield, Eluent AcOEt/PE: 10:90 to 30:70

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.42 – 7.34 (m, 1H), 7.34 – 7.25 (m, 2H), 7.27 – 7.18 (m, 10H), 6.74 (d, *J* = 7.1 Hz, 2H), 3.32 (d, *J* = 12.8 Hz, 2H), 3.23 (d, *J* = 12.6 Hz, 2H), 3.16 (sept, *J* = 6.8 Hz 1H), 0.76 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 183.7, 162.6, 135.4, 130.6, 130.1, 129.8, 128.5, 127.6, 127.4, 126.7, 75.7, 46.2, 43.1, 19.0.

IR: 3030 (w), 1722 (m), 1631 (w), 1495 (w), 1455 (w), 1356 (w), 1342 (w), 1287 (w), 1190 (w), 1094 (w), 1071 (w), 1030 (w), 771 (w), 752 (m), 698 (s).

HRMS: (ESI) calcd for $C_{26}H_{27}N_2O^+$ $[M+H]^+$ 383.2118; found 383.2112.



II-167c

General procedure B

Yield: 34.9 mg, 82% yield, Eluent AcOEt/PE: 10:90 to 30:70

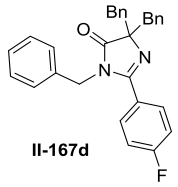
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.25 – 7.14 (m, 11H), 6.91 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.37 (d, *J* = 7.5 Hz, 1H), 6.29 (br. s, 1H), 3.75 (s, 3H), 3.32 (d, *J* = 12.9 Hz, 2H), 3.26 (d, *J* = 13.0 Hz, 2H), 2.81 (t, *J* = 7.2 Hz, 2H), 0.71 – 0.62 (m, 2H), 0.62 – 0.56 (m, 2H), 0.52 (t, *J* = 6.4 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 183.6, 162.1, 159.4, 135.5, 131.3, 130.5, 129.8, 127.8, 126.8, 119.6, 116.5, 112.7, 76.2, 55.4, 43.2, 40.5, 29.9, 19.3, 13.5.

IR: 2957 (w), 1725 (m), 1598 (w), 1580 (w), 1494 (w), 1455 (m), 1354 (m), 1289 (m), 1097 (w), 1046 (m), 793 (w), 750 (m), 715 (m), 700 (s).

HRMS: (ESI) calcd for $C_{28}H_{31}N_2O_2^+$ $[M+H]^+$ 427.2380; found 427.2379.



II-167d

General procedure B

Yield: 24.2 mg, 54% yield, Eluent AcOEt/PE: 10:90 to 30:70

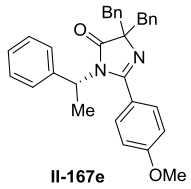
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.26 – 7.22 (m, 10H), 7.09 – 7.01 (m, 1H), 6.99 – 6.92 (m, 2H), 6.88 – 6.80 (m, 2H), 6.71 – 6.63 (m, 2H), 6.09 – 6.02 (m, 2H), 4.03 (s, 2H), 3.39 (d, *J* = 12.9 Hz, 2H), 3.35 (d, *J* = 13.0 Hz, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): 183.4, 163.9 (d, *J* =251.1 Hz), 161.3, 135.6, 135.5, 130.5, 129.8 (d, *J* = 8.7 Hz), 128.5, 128.0, 127.1, 126.2, 125.9, 115.6 (d, *J* = 22.0 Hz), 76.8, 44.2, 43.5.

IR: 3031 (w), 1730 (m), 1630 (w), 1603 (w), 1510 (m), 1455 (w), 1354 (m), 1236 (w), 1124 (m), 1090 (w), 1031 (w), 840 (m), 750 (m), 700 (s).

HRMS: (ESI) calcd for $C_{30}H_{26}FN_2O^+$ $[M+H]^+$ 449.2024; found 449.2017.



II-167e

General procedure B

Yield: 37.5 mg, 79% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: yellow oil

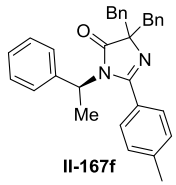
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.34 – 7.26 (m, 5H), 7.24 – 7.17 (m, 5H), 7.13 – 7.05 (m, 1H), 7.04 – 6.96 (m, 2H), 6.64 (d, *J* = 8.6 Hz, 2H), 6.50 (d, *J* = 8.3 Hz, 2H), 6.29 (d, *J* = 7.6 Hz, 2H), 4.59 (q, *J* = 7.2 Hz, 1H), 3.74 (s, 3H), 3.34 (s, 2H), 3.33 (s, 2H), 0.87 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 183.3, 162.6, 160.7, 139.7, 135.4, 135.4, 130.7, 130.5, 129.2, 128.1, 127.8, 127.8, 126.9, 126.8, 126.7, 126.1, 122.9, 113.5, 75.7, 55.2, 50.9, 43.5, 43.4, 16.9.

IR: 2920 (w), 1725 (m), 1626 (w), 1513 (m), 1495 (w), 1455 (w), 1343 (w), 1298 (w), 1252 (s), 1176 (m), 1029 (m), 836 (w), 749 (m), 700 (s).

HRMS: (ESI) calcd for $C_{32}H_{31}N_2O_2^+$ $[M+H]^+$ 475.2380; found 475.2383.

$[\alpha]_D^{25}$= - 9.0 (*c* 1.58, $CHCl_3$)



II-167f

General procedure B

Yield: 33.0 mg, 72% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: yellow oil

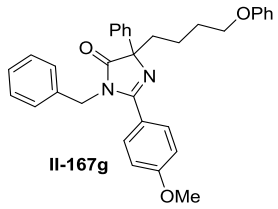
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 5H), 7.12 – 7.05 (m, 1H), 7.02 – 6.97 (m, 2H), 6.96 – 6.89 (m, 2H), 6.50 – 6.43 (m, 2H), 6.31 – 6.25 (m, 2H), 4.55 (q, *J* = 7.2 Hz, 1H), 3.34 (s, 2H), 3.33 (s, 2H), 2.27 (s, 3H), 0.87 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 183.3, 162.9, 140.1, 139.7, 135.5, 130.9, 130.7, 128.9, 128.2, 128.0, 128.0, 127.7, 127.6, 127.0, 126.9, 126.8, 126.3, 75.9, 51.1, 43.6, 21.5, 17.0.

IR: 3030 (w), 1725 (m), 1628 (w), 1495 (w), 1341 (w), 1145 (w), 1093 (w), 821 (w), 748 (m), 699 (s).

HRMS: (ESI) calcd for $C_{32}H_{31}N_2O^+$ $[M+H]^+$ 459.2431; found 459.2432.

$[\alpha]_D^{25}$= - 11.4 (*c* 1.82, $CHCl_3$)



II-167g

General procedure B

Yield: 32.8 mg, 65% yield, Eluent AcOEt/PE: 10:90 to 30:70

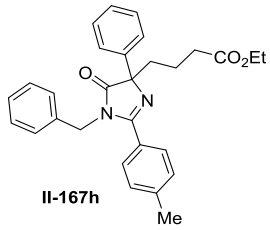
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.80 – 7.73 (m, 2H), 7.50 – 7.46 (m, 2H), 7.38 – 7.36 (m, 2H), 7.35 – 7.26 (m, 2H), 7.26 – 7.24 (m, 1H), 7.21 – 7.19 (m, 3H), 7.05 – 6.97 (m, 2H), 6.97 – 6.88 (m, 3H), 6.88 – 6.81 (m, 2H), 4.75 (d, *J* = 15.8 Hz, 1H), 4.69 (d, *J* = 15.9 Hz, 1H), 3.87 (t, *J* = 6.5 Hz, 2H), 3.85 (s, 3H), 2.36 – 2.18 (m, 2H), 1.84 – 1.70 (m, 2H), 1.50 – 1.37 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 184.5, 162.2, 161.9, 159.1, 139.8, 136.6, 130.1, 129.5, 128.8, 128.6, 127.7, 127.7, 127.1, 126.2, 122.2, 120.6, 114.6, 114.2, 75.3, 67.6, 55.6, 45.4, 40.7, 29.4, 21.1.

IR: 2940 (w), 1726 (m), 1601 (m), 1514 (m), 1496 (m), 1301 (m), 1247 (s), 1174 (m), 1032 (m), 840 (m), 755 (s), 734 (m), 693 (s).

HRMS: (ESI) calcd for $C_{33}H_{33}N_2O_3^+$ $[M+H]^+$ 505.2486; found 505.2484.



II-167h

General procedure B

Yield: 30.9 mg, 63% yield, Eluent AcOEt/PE: 5:95 to 20:80

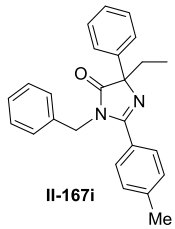
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.72 – 7.64 (m, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.32 – 7.25 (m, 2H), 7.27 – 7.20 (m, 1H), 7.19 – 7.11 (m, 5H), 6.95 – 6.88 (m, 2H), 4.73 (d, *J* = 16.0 Hz, 1 H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 2.28 – 2.17 (m, 3H), 2.12 – 2.03 (m, 1H), 1.64 – 1.49 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 184.0, 173.2, 162.8, 141.6, 139.4, 136.5, 129.5, 128.9, 128.8, 128.6, 128.4, 127.8, 127.7, 127.1, 126.2, 75.1, 60.4, 45.3, 40.0, 34.3, 21.7, 20.0, 14.4.

IR: 2979 (w), 1728 (s), 1622 (w), 1495 (w), 1447 (m), 1377 (m), 1329 (m), 1253 (m), 1179 (m), 1073 (m), 1031 (m), 934 (w), 824 (m), 722 (m), 699 (s).

HRMS: (ESI) calcd for $C_{29}H_{31}N_2O_3^+$ $[M+H]^+$ 455.2329; found 455.2326.



II-167i

General procedure B

Yield: 21.4 mg, 58% yield, Eluent AcOEt/PE: 5:95 to 20:80

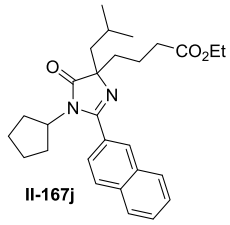
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.84 – 7.69 (m, 2H), 7.43 – 7.34 (m, 4H), 7.32 – 7.27 (m, 1H), 7.24 – 7.21 (m, 5H), 7.03 – 6.98 (m, 2H), 4.75 (d, *J* = 15.8 Hz, 1H), 4.67 (d, *J* = 15.8 Hz, 1H), 2.41 (s, 3H), 2.29 – 2.21 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 184.4, 162.8, 141.6, 139.7, 136.6, 129.5, 128.8, 128.5, 128.4, 127.7, 127.7, 127.2, 126.2, 75.8, 45.3, 34.0, 21.7, 8.8.

IR: 2970 (w), 1728 (s), 1623 (m), 1448 (w), 1377 (m), 1332 (m), 1118 (w), 826 (w), 765 (w), 720 (w), 699 (m).

HRMS: (ESI) calcd for $C_{25}H_{25}N_2O^+$ $[M+H]^+$ 369.1961; found 369.1957.



II-167j

General procedure B

Yield: 36.8 mg, 82% yield, Eluent AcOEt/PE: 5:95 to 20:80

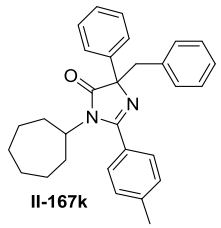
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.08 (s, 1H), 8.00 – 7.88 (m, 3H), 7.64 – 7.53 (m, 3H), 4.20 – 4.02 (m, 3H), 2.28 (t, *J* = 7.6 Hz, 2H), 2.24 – 2.15 (m, 2H), 1.96 – 1.73 (m, 8H), 1.70 – 1.55 (m, 2H), 1.53 – 1.40 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 185.7, 173.3, 163.3, 134.2, 132.9, 128.9, 128.7, 128.5, 128.0, 127.9, 127.8, 127.2, 124.5, 73.7, 60.4, 56.0, 46.2, 38.4, 34.4, 29.3, 29.0, 25.3, 25.2, 24.9, 24.5, 23.6, 18.9, 14.4.

IR: 2955 (w), 2871 (w), 1726 (s), 1619 (w), 1470 (w), 1325 (w), 1281 (w), 1180 (w), 822 (w), 755 (w).

HRMS: (ESI) calcd for $C_{28}H_{37}N_2O_3^+$ $[M+H]^+$ 449.2799; found 449.2799.



II-167k

General procedure B

Yield: 21.8 mg, 50% yield, Eluent AcOEt/PE: 5:95 to 20:80

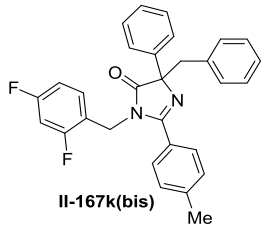
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.92 – 7.81 (m, 2H), 7.40 (dd, *J* = 8.5, 6.8 Hz, 2H), 7.36 – 7.27 (m, 3H), 7.26 – 7.21 (m, 5H), 7.15 – 7.08 (m, 2H), 3.51 (d, *J* = 12.8 Hz, 1H), 3.40 (d, *J* = 13.2 Hz, 1H), 3.36 – 3.27 (m, 1H), 2.40 (s, 3H), 2.04 – 1.88 (m, 1H), 1.83 – 1.73 (m, 1H), 1.61 – 1.49 (m, 2H), 1.43 – 1.33 (m, 4H), 1.16 – 1.01 (m, 2H), 0.98 – 0.84 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 183.1, 163.3, 140.8, 139.8, 135.3, 131.2, 129.4, 128.6, 128.0, 127.8, 127.0, 126.3, 75.5, 56.8, 47.0, 32.3, 31.8, 27.5, 27.4, 25.4, 25.3, 21.7.

IR: 2924 (w), 2858 (w), 1722 (s), 1627 (w), 1495 (w), 1448 (w), 1344 (m), 1272 (w), 1121 (w), 823 (w), 700 (s).

HRMS: (ESI) calcd for $C_{30}H_{33}N_2O^+$ $[M+H]^+$ 437.2587; found 437.2598.



II-167k(bis)

General procedure B

Yield: 30.9 mg, 63% yield, Eluent AcOEt/PE: 5:95 to 20:80

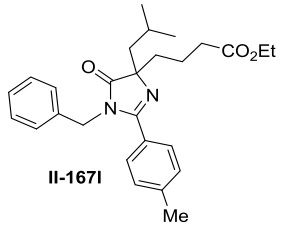
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.00 – 7.84 (m, 2H), 7.47 – 7.40 (m, 2H), 7.38 – 7.31 (m, 3H), 7.30 –7.22 (m, 3H), 7.16 – 7.07 (m, 4H), 6.65 – 6.56 (m, 1H), 6.55 – 6.48 (m, 1H), 6.01 – 5.90 (m, 1H), 4.46 (d, *J* = 16.5 Hz, 1H), 4.34 (d, *J* = 16.6 Hz, 1H), 3.58 (d, *J* = 13.1 Hz, 1H), 3.52 (d, *J* = 13.2 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 183.0, 162.1 (dd, *J* = 248.7, 12.0 Hz), 161.8, 159.6 (dd, *J* = 249.4, 12.0 Hz), 141.3, 139.5, 135.3, 130.9, 129.3, 129.0 (dd, *J* = 9.6, 5.2 Hz), 128.6, 128.0, 127.9, 127.6, 127.1, 126.5, 126.1, 119.0 (dd, *J* = 14.4, 3.7 Hz), 111.5 (dd, *J* = 21.3, 3.6 Hz), 103.5 (t, *J* = 25.4 Hz), 76.3, 46.8, 38.3 (d, *J* = 4.7 Hz), 21.5.

IR: 2928 (w), 1731 (s), 1622 (m), 1607 (m), 1506 (s), 1431 (m), 1382 (m), 1338 (m), 1274 (m), 1140 (m), 1093 (m), 967 (m), 848 (w), 824 (m), 702 (s).

HRMS: (ESI) calcd for $C_{30}H_{25}F_2N_2O^+$ $[M+H]^+$ 467.1929; found 467.1948.



II-167l

General procedure B

Yield: 32.6 mg, 75% yield, Eluent AcOEt/PE: 5:95 to 20:80

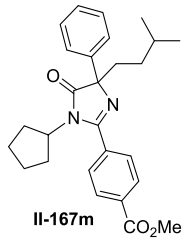
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.8 Hz, 2H), 7.24 – 7.21 (m, 5H), 7.11 – 7.00 (m, 2H), 4.74 (d, *J* = 15.7 Hz, 1H), 4.68 (d, *J* = 15.7 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 2.24 (t, *J* = 7.6 Hz, 2H), 1.95 – 1.76 (m, 4H), 1.59 – 1.50 (m, 2H), 1.48 – 1.38 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 186.1, 173.2, 162.1, 141.5, 136.6, 129.6, 128.8, 128.2, 127.8, 127.5, 127.1, 73.9, 60.4, 46.2, 45.4, 38.1, 34.4, 24.8, 24.4, 23.8, 21.7, 19.2, 14.4.

IR: 2955 (w), 1730 (s), 1623 (w), 1456 (w), 1376 (w), 1355 (w), 1182 (w), 822 (w), 729 (w), 702 (w).

HRMS: (ESI) calcd for $C_{27}H_{35}N_2O_3^+$ $[M+H]^+$ 435.2642; found 435.2649.



II-167m

General procedure B

Yield: 32.9 mg, 76% yield, Eluent AcOEt/PE: 5:95 to 20:80

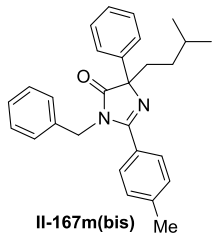
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.3 Hz, 2H), 7.75 – 7.64 (m, 4H), 7.36 (m, 2H), 7.33 – 7.26 (m, 1H), 3.97 (s, 3H), 3.97 – 3.90 (m, 1H), 2.25 – 2.02 (m, 4H), 1.93 – 1.84 (m, 2H), 1.83 – 1.76 (m, 1H), 1.74 – 1.65 (m, 1H), 1.57 – 1.42 (m, 3H), 1.17 – 1.07 (m, 2H), 0.85 (t, *J* = 6.3 Hz, 6H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 183.9, 166.3, 162.9, 139.8, 134.6, 132.4, 130.2, 128.6, 128.5, 127.7, 126.1, 75.4, 55.9, 52.6, 39.2, 32.8, 29.5, 29.4, 28.2, 25.4, 25.4, 22.7, 22.5.

IR: 2952 (w), 2870 (w), 1723 (s), 1606 (w), 1352 (w), 1276 (s), 1106 (m), 1020 (w), 865 (w), 777 (w), 714 (m), 700 (m).

HRMS: (ESI) calcd for $C_{27}H_{33}N_2O_3^+$ $[M+H]^+$ 433.2486; found 433.2502.



II-167m(bis)

General procedure B

Yield: 21.4 mg, 52% yield, Eluent AcOEt/PE: 5:95 to 20:80

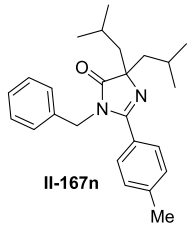
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.86 – 7.75 (m, 2H), 7.51 – 7.38 (m, 4H), 7.37 – 7.31 (m, 1H), 7.29 – 7.23 (m, 5H), 7.05 – 7.00 (m, 2H), 4.79 (d, *J* = 15.8 Hz, 1H), 4.71 (d, *J* = 15.8 Hz, 1H), 2.45 (s, 3H), 2.32 – 2.14 (m, 2H), 1.55 (sept, *J* = 6.6 Hz, 1H), 1.15 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 184.6, 162.3, 141.5, 140.0, 136.6, 129.5, 128.8, 128.5, 128.4, 127.9, 127.7, 127.6, 127.2, 126.2, 75.4, 45.3, 39.1, 33.0, 28.3, 22.7, 22.5, 21.7.

IR: 2954 (w), 2925 (w), 1729 (s), 1623 (w), 1448 (w), 1378 (w), 1329 (w), 826 (w), 722 (w), 699 (m).

HRMS: (ESI) calcd for $C_{28}H_{31}N_2O^+$ $[M+H]^+$ 411.2431; found 411.2445.



II-167n

General procedure B

Yield: 27.9 mg, 74% yield, Eluent AcOEt/PE: 5:95 to 20:80

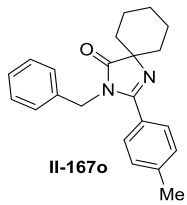
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.40 – 7.32 (m, 2H), 7.26 – 7.21 (m, 5H), 7.09 – 7.00 (m, 2H), 4.70 (s, 2H), 2.40 (s, 3H), 1.86 (dd, *J* = 13.8, 5.8 Hz, 2H), 1.78 (dd, *J* = 13.8, 6.2 Hz, 2H), 1.52 (sept, *J* = 6.6 Hz, 2H), 0.85 (d, *J* = 6.7 Hz, 6H), 0.81 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 186.9, 161.2, 141.3, 136.7, 129.6, 128.7, 128.2, 127.8, 127.7, 127.3, 74.3, 47.5, 45.4, 24.6, 24.5, 24.1, 21.7.

IR: 2954 (w), 2869 (w), 1728 (s), 1623 (w), 1456 (w), 1356 (m), 1329 (m), 1119 (w), 1074 (w), 948 (w), 821 (m), 729 (m), 702 (m).

HRMS: (ESI) calcd for $C_{25}H_{33}N_2O^+$ $[M+H]^+$ 377.2587; found 377.2591.



II-167o

General procedure B

Yield: 18.3 mg, 55% yield, Eluent AcOEt/PE: 5:95 to 20:80

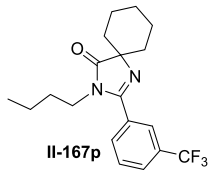
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.33 – 7.28 (m, 2H), 7.28 – 7.21 (m, 3H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.03 – 6.94 (m, 2H), 4.69 (s, 2H), 2.37 (s, 3H), 1.90 – 1.79 (m, 6H), 1.78 – 1.69 (m, 1H), 1.61 (d, *J* = 4.9 Hz, 2H), 1.52 (s, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 187.0, 161.4, 141.2, 136.9, 129.4, 128.8, 128.4, 127.6, 126.9, 70.5, 44.7, 33.6, 25.4, 21.6, 21.6.

IR: 2932 (m), 2854 (w), 2361 (w), 1727 (s), 1624 (w), 1378 (w), 1353 (m), 1329 (w), 981 (w), 824 (w), 723 (w), 697 (w).

HRMS: (ESI) calcd for $C_{22}H_{25}N_2O^+$ $[M+H]^+$ 333.1961; found 333.1957.



II-167p

General procedure B

Yield: 21.5 mg, 61% yield, Eluent AcOEt/PE: 5:95 to 20:80

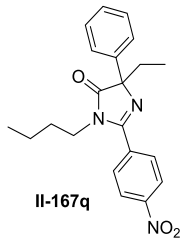
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.79 (m, 2H), 7.65 (t, *J* = 7.8 Hz, 1H), 3.55 – 3.44 (m, 2H), 1.86 – 1.69 (m, 7H), 1.58 – 1.45 (m, 3H), 1.42 – 1.31 (m, 2H), 1.22 – 1.11 (m, 2H), 0.79 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 186.4, 160.1, 131.6 (q, *J* = 33.0 Hz), 131.5, 129.6, 127.7, 127.6 (br. s), 125.2 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.6 Hz) 122.3, 119.6, 70.9, 41.0, 33.5, 31.0, 25.3, 21.6, 19.7, 13.6.

IR: 2934 (w), 2860 (w), 1729 (m), 1447 (w), 1329 (s), 1279 (m), 1237 (m), 1169 (m), 1129 (s), 1072 (m), 970 (w), 910 (w), 811 (w), 699 (w).

HRMS: (ESI) calcd for $C_{19}H_{24}F_3N_2O^+$ $[M+H]^+$ 353.1835; found 353.1838.



II-167q

General procedure B

Yield: 16.1 mg, 44% yield, Eluent AcOEt/PE: 5:95 to 20:80

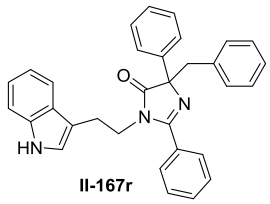
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.44 – 8.38 (m, 2H), 7.90 – 7.85 (m, 2H), 7.72 – 7.67 (m, 2H), 7.42 – 7.34 (m, 3H), 7.33 – 7.27 (m, 1H), 3.64 – 3.44 (m, 2H), 2.34 – 2.09 (m, 2H), 1.48 – 1.28 (m, 2H), 1.21 – 1.10 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.78 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 183.7, 160.9, 149.4, 139.1, 136.2, 129.4, 128.7, 127.9, 126.0, 124.3, 76.3, 41.5, 34.2, 31.1, 19.9, 13.6, 8.7.

IR: 2962 (w), 2934 (w), 2362 (w), 1729 (s), 1594 (m), 1524 (s), 1350 (s), 1075 (w), 864 (m), 854 (m), 760 (m), 703 (s).

HRMS: (ESI) calcd for $C_{21}H_{24}N_3O_3^+$ $[M+H]^+$ 366.1812; found 366.1825.



II-167r

General procedure B

Yield: 30.9 mg, 63% yield, Eluent AcOEt/PE: 10:90 to 30:70

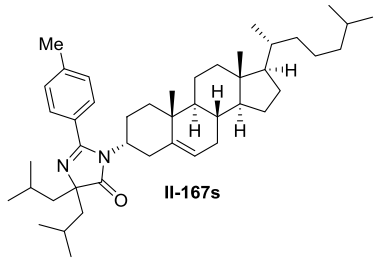
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.97 – 7.84 (m, 3H), 7.51 – 7.43 (m, 1H), 7.47 – 7.39 (m, 2H), 7.40 – 7.31 (m, 5H), 7.30 – 7.21 (m, 4H), 7.19 – 7.11 (m, 2H), 7.10 (ddd, *J* = 8.2, 5.7, 2.4 Hz, 1H), 6.98 – 6.88 (m, 2H), 6.59 (br. s, 1H), 3.60 (d, *J* = 13.0 Hz, 1H), 3.54 – 3.32 (m, 3H), 3.49 (d, *J* = 13.0 Hz, 1H), 2.53 (ddd, *J* = 14.5, 10.0, 6.4 Hz, 1H), 2.23 (ddd, *J* = 14.5, 10.0, 5.3 Hz, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.9, 162.7, 139.2, 136.2, 135.2, 131.0, 130.8, 128.8, 128.7, 128.0, 127.9, 127.2, 127.0, 126.3, 122.2, 122.1, 119.5, 118.4, 111.7, 111.2, 76.2, 47.1, 41.8, 24.0.

IR: 3059 (w), 1723 (m), 1627 (w), 1597 (w), 1496 (w), 1448 (w), 1339 (w), 772 (w), 738 (s), 698 (s).

HRMS: (ESI) calcd for $C_{32}H_{28}N_3O^+$ $[M+H]^+$ 470.2227; found 470.2244.



II-167s

General procedure B

Yield: 34.0 mg, 52% yield, Eluent AcOEt/PE: 5:95 to 20:80

Aspect: yellow oil

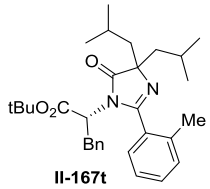
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.48 – 7.34 (m, 2H), 7.30 – 7.26 (m, 2H), 5.28 (br. s, 1H), 4.04 – 3.91 (m, 1H), 2.59 – 2.47 (m, 1H), 2.42 (s, 3H), 2.37 – 2.29 (m, 1H), 2.20 – 2.10 (m, 1H), 2.02 – 1.90 (m, 3H), 1.85 – 1.68 (m, 7H), 1.61 – 1.44 (m, 6H), 1.41 – 1.30 (m, 2H), 1.29 – 1.20 (m, 2H), 1.19 – 0.98 (m, 10H), 0.92 – 0.79 (m, 25H), 0.66 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 186.3, 162.6, 140.7, 138.9, 129.6, 128.5, 127.9, 123.0, 73.8, 56.9, 56.2, 51.8, 48.2, 47.7, 47.7, 42.6, 39.9, 39.6, 36.4, 36.3, 36.0, 35.4, 34.5, 32.1, 31.7, 28.4, 28.2, 24.7, 24.7, 24.6, 24.6, 24.5, 24.3, 24.3, 24.0, 24.0, 23.0, 22.7, 21.8, 21.7, 21.2, 18.8, 12.1.

IR: 2952 (s), 2934 (s), 2868 (m), 1730 (s), 1625 (w), 1466 (w), 1352 (w), 1169 (w), 1113 (w), 820 (w).

HRMS: (ESI) calcd for $C_{44}H_{69}N_2O^+$ $[M+H]^+$ 641.5404; found -.0005.

$[\alpha]_D^{25}$= - 1.9 (*c* 1.88, $CHCl_3$)



II-167t

General procedure B

Yield: 30.9 mg, 63% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: yellow oil

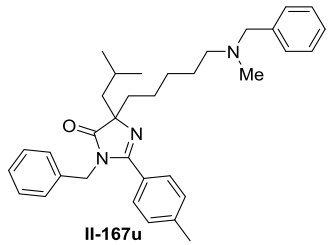
^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.30 (m, 1H), 7.23 – 7.17 (m, 4H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.96 – 6.88 (m, 2H), 6.57 (br. s, 1H), 4.04 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.38 (dd, *J* = 14.3, 10.4 Hz, 1H), 3.32 (dd, *J* =14.3, 5.0 Hz, 1H), 2.03 (s, 3H), 1.80 – 1.75 (m, 3H), 1.71 – 1.61 (m, 2H), 1.56 – 1.50 (m, 1H), 1.49 (s, 9H), 0.94 (d, J = 6.6 Hz, 3H), 0.92 (d, J =6.6 Hz, 6H), 0.88 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 185.9, 167.9, 160.6, 137.4, 137.3, 130.6, 130.2, 129.6, 129.0, 128.8, 128.6, 127.0, 125.8, 83.1, 74.9, 58.5, 46.0, 45.9, 34.4, 28.1, 25.0, 24.9, 24.8, 24.8, 24.5, 24.4, 19.2.

IR: 2953 (w), 1727 (s), 1633 (w), 1456 (w), 1365 (m), 1277 (m), 1155 (s), 847 (w), 768 (w), 749 (w), 701 (m).

HRMS: (ESI) calcd for $C_{31}H_{43}N_2O_3^+$ $[M+H]^+$ 491.3268; found 491.3268.

$[\alpha]_D^{25}$= - 52.0 (*c* 2.65, $CHCl_3$)



II-167u

General procedure B

Yield: 26 mg, 51% yield, Eluent AcOEt/PE: 40:60 to 80:20

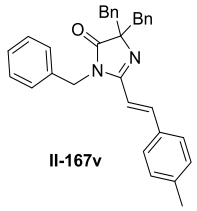
Aspect: yellow oil

^{1}H NMR (400.13 MHz, MeOD): δ 7.45 – 7.36 (m, 7H), 7.36 – 7.32 (m, 2H), 7.24 – 7.21 (m, 3H), 7.00 – 6.96 (m, 2H), 4.78 (d, *J* = 15.6 Hz, 1H), 4.72 (d, *J* = 15.6 Hz, 1H), 3.90 (s, 2H), 2.74 – 2.64 (m, 2H), 2.47 (s, 3H), 2.43 (s, 3H), 1.88 – 1.77 (m, 4H), 1.61 – 1.55 (m, 2H), 1.53 – 1.45 (m, 1H), 1.32 – 1.25 (m, 2H), 1.21 – 1.13 (m, 1H), 1.08 – 0.99 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100.62 MHz, MeOD): δ 187.1, 164.8, 143.4, 137.7, 131.4, 130.7, 129.9, 129.9, 129.6, 129.2, 128.9, 128.9, 127.8, 75.1, 61.9, 57.5, 47.4, 46.0, 41.2, 39.6, 27.9, 26.2, 25.7, 24.7, 24.3, 24.1, 21.5.

IR: 2946 (w), 2365 (w), 1728 (s), 1623 (w), 1456 (w), 1377 (w), 1356 (w), 1329 (w), 1118 (w), 822 (w), 743 (w), 731 (w), 700 (m).

HRMS: (ESI) calcd for $C_{34}H_{44}N_3O^+$ $[M+H]^+$ 510.3479; found 510.3481.



II-167v

General procedure B

Yield: 36.7 mg, 78% yield, Eluent AcOEt/PE: 10:90 to 30:70

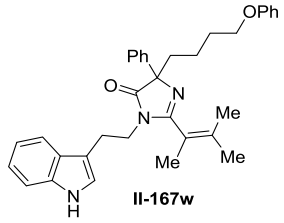
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.54 (br s., 1H), 7.25 (d, *J* = 4.1 Hz, 4H), 7.24 – 7.17 (m, 6H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 7.6 Hz, 3H), 7.04 (t, *J* = 7.5 Hz, 2H), 6.18 (d, *J* = 7.6 Hz, 2H), 5.84 (d, *J* = 15.9 Hz, 1H), 4.22 (s, 2H), 3.44 – 3.28 (m, 4H), 2.32 (s, 3H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 182.4, 159.2, 140.2, 138.9, 135.3, 132.0, 130.3, 129.5, 128.7, 128.5, 127.9, 127.6, 127.2, 126.8, 125.7, 112.2, 76.3, 43.5, 42.8, 21.4.

IR: 3029 (w), 2360 (w), 1730 (m), 1639 (w), 1593 (m), 1495 (w), 1455 (w), 1387 (w), 1356 (m), 1183 (w), 976 (w), 807 (w), 757 (w), 701 (s).

HRMS: (ESI) calcd for $C_{33}H_{31}N_2O^+$ $[M+H]^+$ 471.2431; found 471.2452.



II-167w

General procedure B

Yield: 30.1 mg, 58% yield, Eluent AcOEt/PE: 20:80 to 40:60

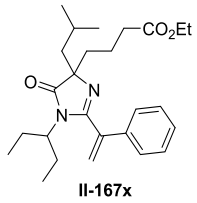
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.76 – 7.71 (m, 1H), 7.71 – 7.66 (m, 2H), 7.49 – 7.42 (m, 1H), 7.41 – 7.33 (m, 2H), 7.33 – 7.27 (m, 3H), 7.26 – 7.22 (m, 1H), 7.20 – 7.14 (m, 1H), 7.11 – 7.03 (m, 1H), 6.97 – 6.90 (m, 1H), 6.84 (d, *J* = 8.1 Hz, 2H), 6.70 (s, 1H), 3.88 (t, *J* = 6.3 Hz, 2H), 3.74 – 3.58 (m, 2H), 3.09 – 2.92 (m, 2H), 2.15 (dq, *J* = 15.3, 7.9, 7.2 Hz, 2H), 1.79 – 1.72 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.53 (s, 3H), 1.47 – 1.36 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 184.1, 165.2, 159.1, 140.1, 137.4, 136.5, 129.6, 128.5, 127.6, 127.2, 126.1, 122.8, 122.3, 120.7, 119.6, 118.4, 114.6, 111.7, 111.4, 74.9, 67.6, 41.8, 40.4, 29.4, 24.4, 22.3, 21.2, 20.0, 17.3.

IR: 2944 (w), 1727 (s), 1600 (m), 1496 (m), 1448 (m), 1358 (m), 1356 (m), 1246 (s), 1109 (w), 1035 (w), 758 (s), 746 (s), 694 (m).

HRMS: (ESI) calcd for $C_{34}H_{38}N_3O_2^+$ $[M+H]^+$ 520.2959; found 520.2663.



II-167x

General procedure B

Yield: 23.4 mg, 55% yield, Eluent AcOEt/PE: 20:80 to 40:60

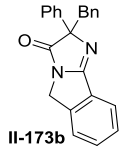
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.56 – 7.31 (m, 5H), 5.86 (s, 1H), 5.76 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.12 – 3.00 (m, 1H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.93 – 1.80 (m, 2H), 1.79 – 1.62 (m, 6H), 1.61 – 1.48 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.93 (d, *J* = 6.2 Hz, 3H), 0.58 (t, *J* = 7.4 Hz, 3H), 0.57(t, *J* = 7.4 Hz, 3H)

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 185.9, 173.1, 163.6, 140.9, 136.5, 129.2, 129.1, 126.7, 121.5, 74.0, 60.4, 59.8, 46.1, 37.7, 34.6, 24.9, 24.8, 24.7, 24.6, 24.3, 19.7, 14.4, 11.5.

IR: 2962 (w), 2934 (w), 2875 (w), 2363 (w), 1726 (s), 1609 (w), 1461 (m), 1350 (m), 1214 (m), 1181 (m), 1072 (w), 1030 (w), 924 (w), 780 (w), 700 (m).

HRMS: (ESI) calcd for $C_{26}H_{39}N_2O_3^+$ $[M+H]^+$ 427.2955; found 427.2961.



II-173b

General procedure B

Yield: 14.9 mg, 44% yield, Eluent AcOEt/PE: 10:90 to 30:70

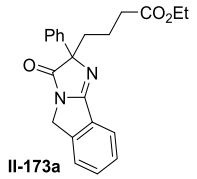
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.09 (m, *J* = 16.6 Hz, 1H), 7.91 – 7.82 (m, 2H), 7.59 – 7.48 (m, 2H), 7.45 – 7.36 (m, 3H), 7.35 – 7.31 (m, 1H), 7.31 – 7.26 (m, 2H), 7.14 – 7.09 (m, 2H), 7.08 – 7.03 (m, 1H), 4.47 (d, *J* = 16.5 Hz, 1H), 4.23 (d, *J* = 16.4 Hz, 1H), 3.57 (d, *J* = 13.2 Hz, 1H), 3.51 (d, *J* = 13.6 Hz, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 179.3, 165.1, 145.4, 135.0, 133.1, 130.5, 129.1, 128.9, 128.7, 128.2, 128.1, 127.8, 127.1, 126.3, 126.2, 124.5, 84.5, 46.7, 44.6.

IR: 3060 (w), 2925 (w), 1724 (s), 1448 (m), 1343 (m), 1308 (w), 736 (m), 721 (m), 700 (s).

HRMS: (ESI) calcd for $C_{23}H_{19}N_2O^+$ $[M+H]^+$ 339.1492; found 339.1498.



II-173a

General procedure B

Yield: 17.4 mg, 48% yield, Eluent AcOEt/PE: 10:90 to 30:70

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.77 – 7.69 (m, 2H), 7.65 – 7.60 (m, 1H), 7.58 – 7.55 (m, 1H), 7.54 – 7.49 (m, 1H), 7.38 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 4.74 (d, *J* = 16.4 Hz, 1H), 4.62 (d, *J* = 16.4 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 3H), 2.33 – 2.25 (m, 2H), 2.26 – 2.12 (m, 2H), 1.70 – 1.60 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H).

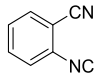
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 179.5, 173.3, 165.9, 145.6, 139.6, 133.0, 129.1, 128.7, 128.6, 127.9, 126.0, 124.7, 123.9, 83.8, 60.5, 44.8, 39.8, 34.2, 20.0, 14.3.

IR: 2930 (w), 1727 (s), 1664 (m), 1447 (w), 1337 (m), 1252 (w), 1180 (m), 1159 (m), 1033 (w), 737 (m), 700 (m).

HRMS: (ESI) calcd for $C_{22}H_{23}N_2O_3^+$ $[M+H]^+$ 363.1703; found 363.1701.

Chapter 4

Characterization data



II-258

Yield: 40% over two steps

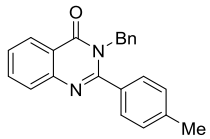
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.77 – 7.69 (m, 1H), 7.68 – 7.62 (m, 1H), 7.57 – 7.45 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 171.6, 133.9, 133.3, 129.8, 128.7 (t, *J* = 12.9 Hz), 127.5, 114.6, 111.1.

IR: 2234 (w), 2124 (s), 1711 (w), 1668 (w), 1594 (w), 1485 (w), 1453 (m), 766 (s), 738 (s), 714 (m).

HRMS: (ESI) calcd for $C_8H_5N_2^+$ $[M+H]^+$ 129.0447; found 129.0446.



II-170a

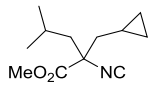
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.81 (s, 3H), 2.01 – 1.81 (m, 3H), 1.76 (dd, *J* = 13.6, 4.8 Hz, 1H), 1.66 – 1.56 (m, 1H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.93 – 0.87 (m, 1H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.66 – 0.52 (m, 1H), 0.50 – 0.41 (m, 1H), 0.22 – 0.14 (m, 1H), 0.09 – -0.01 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.1, 159.9, 67.9, 53.3, 47.2, 45.7, 25.1, 23.9, 22.1, 6.1, 4.0, 4.0.

IR: 2361 (w), 2341 (w), 1617 (s), 1579 (s), 1477 (m), 1388 (m), 1145 (w), 952 (w), 770 (m), 730 (m).

HRMS: (ESI) calcd for $C_{22}H_{18}N_2O$ [M+] 326.1419; found 326.1650.



II-228a

Yield: 82% yield

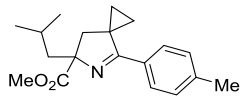
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.81 (s, 3H), 2.01 – 1.81 (m, 3H), 1.76 (dd, *J* = 13.6, 4.8 Hz, 1H), 1.66 – 1.56 (m, 1H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.93 – 0.87 (m, 1H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.66 – 0.52 (m, 1H), 0.50 – 0.41 (m, 1H), 0.22 – 0.14 (m, 1H), 0.09 – -0.01 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.1, 159.9, 67.9, 53.3, 47.2, 45.7, 25.1, 23.9, 22.1, 6.1, 4.0, 4.0.

IR: 2957 (m), 2362 (w), 1745 (s), 1625 (w), 1436 (w), 1267 (m), 1206 (m), 1013 (w).

HRMS: (ESI) calcd for $C_{15}H_{22}N_2NaO_4^+$ [M+Na]$^+$ 317.1472; found 317.1476.



II-290a

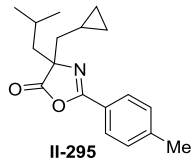
Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.31 – 7.27 (m, 2H), 7.16 – 7.09 (m, 2H), 3.76 (s, 3H), 2.65 (d, *J* = 12.9 Hz, 1H), 2.34 (s, 3H), 2.07 (d, *J* = 12.9 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.89 – 1.80 (m, 2H), 1.18 – 1.11 (m, 1H), 1.08 – 1.01 (m, 1H), 0.96 (s, 3H), 0.95 (s, 3H), 0.95 – 0.84 (m, 2H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 177.9, 175.6, 139.5, 130.7, 129.0, 127.7, 79.2, 52.4, 48.1, 43.6, 32.2, 25.2, 24.2, 24.0, 21.5, 13.1, 12.5.

IR: 2951 (w), 1732 (s), 1596 (w), 1451 (w), 1359 (w), 1221 (m), 1133 (w), 819 (w).

HRMS: (ESI) calcd for $C_{19}H_{26}NO_2^+$ [M+H]$^+$ 300.1958; found 300.1961.



II-295

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.28 (m, 2H), 2.44 (s, 3H), 2.03 (dd, *J* = 13.9, 5.9 Hz, 1H), 1.94 – 1.75 (m, 2H), 1.69 – 1.59 (m, 2H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.65 – 0.54 (m, 1H), 0.38 – 0.32 (m, 2H), 0.10 (ddd, *J* = 8.8, 5.1, 1.3 Hz, 2H).

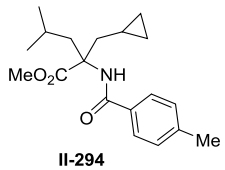
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 181.7, 159.9, 143.4, 129.7, 128.0, 123.5, 73.7, 46.4, 43.8, 25.1, 24.2, 23.3, 21.8, 5.7, 4.1, 3.8.

IR: 2957 (w), 1816 (s), 1735 (w), 1654 (s), 1316 (w), 1302 (w), 1181 (w), 1047 (m), 988 (m), 885 (w), 729 (w).

HRMS: (ESI) calcd for $C_{18}H_{23}NO_2$ [M+] 285.1723; found 285.1724.

(m), 1698 (w), 1651 (s), 1608 (w), 1330 (m), 1244 (s), 1179 (w), 758 (w).

HRMS: (ESI) calcd for $C_{18}H_{23}NO_2$ [M+] 285.1723; found 285.1724.



II-294

Aspect: yellow oil

^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.78 – 7.69 (m, 2H), 7.46 (s, 1H), 7.29 – 7.21 (m, 2H), 3.82 (s, 3H), 2.78 (dd, *J* = 14.1, 5.9 Hz, 1H), 2.67 (dd, *J* = 14.0, 5.1 Hz, 1H), 2.40 (s, 3H), 1.71 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.65 – 1.56 (m, 2H), 1.55 – 1.47 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.58 – 0.46 (m, 1H), 0.40 – 0.25 (m, 2H), 0.10 – 0.02 (m, 1H), -0.04 – -0.15 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 176.2, 166.2, 141.9, 132.6, 129.4, 127.0, 65.0, 52.6, 43.7, 40.8, 24.9, 24.0, 22.6, 21.6, 6.3, 3.7, 3.6.

IR: 3418 (w), 2955 (w), 1730 (m), 1664 (s), 1494 (s), 1445 (m), 1232 (s), 1192 (m), 830 (m), 750 (s).

HRMS: (ESI) calcd for $C_{19}H_{28}NO_3^+$ $[M+H]^+$ 318.2064; found 318.2065.

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Curriculum Vitae

Education

2013-2017: **PhD student** under the supervision of Prof. Dr. J. Zhu – LSPN – EPFL, Lausanne (Switzerland) (Private Thesis defense plan on 27.09.2017).

- Development of catalytic enantioselective transformation and multicomponent reaction.
- Teaching assistant for exercises and practical courses in chemistry.
- Supervision of an apprentice student during 1 year.

2012-2013: **Master of Research Degree** in Organic Chemistry at the University of Caen (France).

2010-2013: **Engineer's degree** from ENSICAEN (Caen, France), speciality Chemistry and Materials, option Chemistry.

2010-2008: **D.U.T** in Chemistry (Technical University Diploma) at the University of Le Mans (France).

2008: **Baccalauréat** in Science (French secondary school diploma) specialised in Physics and Chemistry at Lycée Henry Bergson (Angers, France).

Work Experience

2013: **6 months placement (March – August):**

University of Southampton (England) under the supervisition of Prof. D. Harrowven (INTTEREG fellowship).

- Diastereoselective decarboxylation-protonation of peptides.

2012: **4 months placement (April – July):**

University of Toronto (Canada) under the supervision of Prof. M. Lautens and Dr. D. Petrone.

- Diastereoselective palladium-catalyzed carboiodination for the synthesis of chromans and isochromans.

Project of 3 months at ENSICAEN (January – March):

- Synthesis of fluorosulfones via Julia-Kocienski reaction.

2010: **2.5 months placement (April – June):**

Institut Curie (Paris, France) under the supervision of Dr. V. Semetey.

- Synthesis of amphiphilic and photopolymerisable molecules.

Qualifications and Skills

Computer Science:

Control of Chemdraw, Excel, Word, Powerpoint, MestReNova, Mercury.

Languages:

French: Mother tongue.

English: Excellent level (B2).

Spanish: Intermediate level (A2).

Hobbies and Interests

- Organiser and programme planner of music festival (No Man's Land Festival edition 2009, 2010, 2011 and 2012 at Chalonnes sur Loire, 49290, France).
- Have been playing guitar bass for 6 years (4 years in a band).
- Climbing, skiing and hiking.

Publications

Isocyanide chemistry

- A. Clemenceau, Q. Wang, J. Zhu, *Org. Lett.* **2017**, *DOI:* 10.1021/acs.orglett.7b02334
- A. Clemenceau, Q. Wang, J. Zhu, *manuscript in preparation*

Organocatalysis

- A. Clemenceau, Q. Wang, J. Zhu, *Chem. Eur. J.*, **2016**, *22*, 18368.

Palladium-catalyzed chemistry

- D. Petrone, H. Malik, A. Clemenceau, M. Lautens, *Org. Lett.* **2012**, *14*, 4806.